Systematic review and meta-analysis of genetic risk factors for neuropathic pain

Veluchamy, Abirami; Hébert, Harry L.; Meng, Weihua; Palmer, Colin N. A.; Smith, Blair H.

Published in:
Pain

DOI:
10.1097/j.pain.0000000000001164

Publication date:
2018

Document Version
Peer reviewed version

PAIN

A systematic review and meta-analysis of genetic risk factors for neuropathic pain

--Manuscript Draft--

Manuscript Number:	PAIN-D-17-00936R2
Article Type:	Comprehensive Review
Section/Category:	Genetics/Pharmacology
Keywords:	Neuropathic pain, Genetic risk factor, Polymorphisms, Genome-wide association studies, Candidate gene association studies, Systematic review, Meta-analysis.
Corresponding Author:	Blair Hamilton Smith, MD, MEd, FRCGP, FFPMRCA, FRCP University of Dundee DUNDEE, UNITED KINGDOM
First Author:	Abirami Veluchamy, BSc
Order of Authors:	Abirami Veluchamy, BSc
	Harry Hébert, BSc PhD
	Weihua Meng, MBBS, MSc, PhD
	Colin Palmer, BSc, PhD
	Blair Hamilton Smith, MD, MEd, FRCGP, FFPMRCA, FRCP
Abstract:	Neuropathic pain (NP) is an increasingly common chronic pain state and a major health burden, affecting approximately 7-10% of the general population. Emerging evidence suggests that genetic factors could partially explain individual susceptibility to NP and the estimated heritability in twins is 37%. The aim of this study was to systematically review and summarize the studies in humans that have investigated the influence of genetic factors associated with NP. We conducted a comprehensive literature search and performed meta-analyses of all the potential genetic variants associated with NP. We reviewed 29 full-text articles and identified 28 genes that were significantly associated with NP, mainly involved in neurotransmission, immune response, and metabolism. Genetic variants in HLA genes, COMT, OPRM1, TNFA, IL6, and GCH1, were found to have an association with NP in more than one study. In the meta-analysis, polymorphisms in HLA-DRB1*13 (OR,2.96; CI,1.93-4.56), HLA-DRB1*04 (OR,1.40; CI, 1.02-1.93), HLA-DQB1*03 (OR,2.86; CI,1.57-5.21), HLA-A*33 (OR,2.32; CI,1.42-3.80), and HLA-B*44 (OR,3.17; CI,2.22-4.55) were associated with significantly increased risk of developing NP whereas HLA-A*02 (OR,0.64; CI,0.47-0.87) conferred reduced risk and neither rs1799971 in OPRM1 (OR, 0.55; CI, 0.27-1.11) nor rs4680 in COMT (OR, 0.95; CI, 0.81-1.13) were significantly associated with NP. These findings demonstrate an important and specific contribution of genetic factors to the risk of developing NP. However, large-scale replication studies are required to validate these candidate genes. Our review also highlights the need for genome-wide association studies with consistent case definition to elucidate the genetic architecture underpinning NP.

Abstract

Neuropathic pain (NP) is an increasingly common chronic pain state and a major health burden, affecting approximately 7-10% of the general population. Emerging evidence suggests that genetic factors could partially explain individual susceptibility to NP and the estimated heritability in twins is 37%. The aim of this study was to systematically review and summarize the studies in humans that have investigated the influence of genetic factors associated with NP. We conducted a comprehensive literature search and performed meta-analyses of all the potential genetic variants associated with NP. We reviewed 29 full-text articles and identified 28 genes that were significantly associated with NP, mainly involved in neurotransmission, immune response, and metabolism. Genetic variants in *HLA* genes, *COMT*, *OPRM1, TNFA, IL6,* and *GCH1,* were found to have an association with NP in more than one study. In the meta-analysis, polymorphisms in *HLA-DRB1*13* (OR,2.96; CI,1.93-4.56), *HLA-DRB1*04* (OR,1.40; CI, 1.02-1.93), *HLA-DQB1*03* (OR,2.86; CI,1.57-5.21), *HLA-A*33* (OR,2.32; CI,1.42-3.80), and *HLA-B*44* (OR,3.17; CI,2.22-4.55) were associated with significantly increased risk of developing NP whereas *HLA-A*02* (OR,0.64; CI,0.47-0.87) conferred reduced risk and neither rs1799971 in *OPRM1* (OR, 0.55; CI, 0.27-1.11) nor rs4680 in *COMT* (OR, 0.95; CI, 0.81-1.13) were significantly associated with NP. These findings demonstrate an important and specific contribution of genetic factors to the risk of developing NP. However, large-scale replication studies are required to validate these candidate genes. Our review also highlights the need for genome-wide association studies with consistent case definition to elucidate the genetic architecture underpinning NP.

Title Page

A systematic review and meta-analysis of genetic risk factors for neuropathic pain

Abirami Veluchamy[1], Harry L. Hébert[1], Weihua Meng[1], Colin N.A. Palmer[2] and Blair H. Smith[1]*

[1]Division of Population Health Sciences, University of Dundee, Ninewells Hospital and Medical School, Dundee DD2 4RB - Scotland, United Kingdom and [2] Pat Macpherson Centre for Pharmacogenetics and Pharmacogenomics, Division of Molecular and Clinical Medicine, University of Dundee, Ninewells Hospital and Medical School, Dundee DD1 9SY - Scotland, United Kingdom

*Corresponding author: Blair H. Smith, Chronic pain group, Division of Population Health Sciences, University of Dundee, Ninewells Hospital and Medical School, Dundee DD2 4RB - Scotland, United Kingdom. Phone: +44-1382-383728. Email: b.h.smith@dundee.ac.uk

Number of text pages (include figures and tables): 50

Number of figures: 6

Number of tables: 3

Number of supplementary tables: 5

Number of supplementary figures: 9

Word count: Abstract – 243; Main text - 5844

Title Page

A systematic review and meta-analysis of genetic risk factors for neuropathic pain

Abirami Veluchamy[1], Harry L. Hébert[1], Weihua Meng[1], Colin N.A. Palmer[2] and Blair H. Smith[1]*

[1]Division of Population Health Sciences, University of Dundee, Ninewells Hospital and Medical School, Dundee DD2 4RB - Scotland, United Kingdom and [2] Pat Macpherson Centre for Pharmacogenetics and Pharmacogenomics, Division of Molecular and Clinical Medicine, University of Dundee, Ninewells Hospital and Medical School, Dundee DD1 9SY - Scotland, United Kingdom

*Corresponding author: Blair H. Smith, Chronic pain group, Division of Population Health Sciences, University of Dundee, Ninewells Hospital and Medical School, Dundee DD2 4RB - Scotland, United Kingdom. Phone: +44-1382-383728. Email: b.h.smith@dundee.ac.uk

Number of text pages (include figures and tables): 50

Number of figures: 6

Number of tables: 3

Number of supplementary tables: 5

Number of supplementary figures: 9

Word count: Abstract – 243; Main text - 5844

A systematic review and meta-analysis of genetic risk factors for neuropathic pain

Abstract

Neuropathic pain (NP) is an increasingly common chronic pain state and a major health burden, affecting approximately 7-10% of the general population. Emerging evidence suggests that genetic factors could partially explain individual susceptibility to NP and the estimated heritability in twins is 37%. The aim of this study was to systematically review and summarize the studies in humans that have investigated the influence of genetic factors associated with NP. We conducted a comprehensive literature search and performed meta-analyses of all the potential genetic variants associated with NP. We reviewed 29 full-text articles and identified 28 genes that were significantly associated with NP, mainly involved in neurotransmission, immune response, and metabolism. Genetic variants in *HLA* genes, *COMT*, *OPRM1, TNFA, IL6,* and *GCH1,* were found to have an association with NP in more than one study. In the meta-analysis, polymorphisms in *HLA-DRB1*13* (OR,2.96; CI,1.93-4.56), *HLA-DRB1*04* (OR,1.40; CI, 1.02-1.93), *HLA-DQB1*03* (OR,2.86; CI,1.57-5.21), *HLA-A*33* (OR,2.32; CI,1.42-3.80), and *HLA-B*44* (OR,3.17; CI,2.22-4.55) were associated with significantly increased risk of developing NP whereas *HLA-A*02* (OR,0.64; CI,0.47-0.87) conferred reduced risk and neither rs1799971 in *OPRM1* (OR, 0.55; CI, 0.27-1.11) nor rs4680 in *COMT* (OR, 0.95; CI, 0.81-1.13) were significantly associated with NP. These findings demonstrate an important and specific contribution of genetic factors to the risk of developing NP. However, large-scale replication studies are required to validate these candidate genes. Our review also highlights the need for genome-wide association studies with consistent case definition to elucidate the genetic architecture underpinning NP.

Keywords

Neuropathic pain, Genetic risk factor, Polymorphisms, Genome-wide association studies, Candidate gene association studies, Systematic review, Meta-analysis.

Introduction

Neuropathic pain (NP) is an increasingly common chronic pain state, arising as a result of a lesion or disease affecting the somatosensory system [48,68]. NP is a complex condition with distinct symptoms and has a great impact on health-related quality of life, sleep, mood and anxiety [15,60]. NP affects approximately 7-10% of the general population [4,27], 20-26.4% of individuals with diabetes [5,11], and 10-20% of individuals following herpes zoster in the UK [24,37,76]. Up to 37% of individuals with low back pain [22,54] and 40% of people after surgery [36] suffer from NP. Studies have found that NP affects approximately 8.1 and 17.9% of the Canadian population [67,70]. Inoue *et al* reported that the prevalence of NP is lower (3.2%) in the East Asian population [34].

Genetic susceptibility, as well as environmental factors such as sociodemographic, psychological, clinical, and lifestyle factors, are known to contribute to the risk of developing NP [21,26,41]. Evidence from human genetic studies have shown that some rare NP disorders including congenital sensitivity to pain with anhidrosis, erythromelalgia, and paroxysmal extreme pain disorder are monogenic, caused by mutations in a single gene, *SCN9A* [14,17,33,77]. It has been proposed that the contribution of multiple genes can help to understand why some individuals are susceptible to chronic NP after nerve injury or disease while others are not. Initially, several animal model studies established that NP is partially heritable [12,13] and show the existence of gene-environment interactions in NP susceptibility. Recently, a twins study from the UK reported an estimated heritability of NP of 37% [50] suggesting that genetic factors have the potential to determine a significant proportion of an individual's predisposition to NP. A recent genome-wide associated study (GWAS) also found that NP had a heritable component (11%) in a diabetic population [47]. Several genetic association studies have found variants associated with the risk of developing NP in different conditions as well as affecting pain severity. However, the underlying genetic mechanisms contributing to NP remain elusive due to inconsistent results and lack of validation in the current evidence.

Identifying genetic factors for NP and summarising the results from all studies to date will help to confirm known potential genetic risk variants underlying NP which may provide useful biomarkers for clinical prognosis and pharmacological targets. We therefore performed a comprehensive literature-based systematic review to identify studies of genetic risk factors of NP in humans. This

will help to determine the level of evidence by performing a meta-analysis of each gene association with NP and to explore the functional annotation of identified genetic variants.

Methods

Search strategy

The systematic review protocol was registered in the international prospective register of systematic reviews (PROSPERO registration number CRD42016043523) [71]. Literature searches and meta-analysis were conducted and reported according to the Preferred Reporting Items of Systematic reviews and Meta-analyses (PRISMA) guidelines [49]. We conducted a comprehensive literature search limited to human studies using electronic databases including PubMed, MEDLINE, EMBASE, SCOPUS and Web of Science from January 1996 to July 2016. This was based on a previous systematic review search strategy [28] and we validated the search terms using the pre-selected articles. The search terms used for all five databases included terms related to neuropathic pain, genetic factors and study design. These keywords were combined using Boolean operators (see Supplementary Table S1). The Human pain gene database (http://hpgl.ca/hpgdb/) was searched for any additional studies using the following keywords: neuropathic, post-operative, diabetic, sciatica, and multiple sclerosis.

Study criteria

All genetic studies including molecular genetics findings, candidate gene association studies (CGAS), and GWAS focussing on genetic factors influencing the risk of developing NP in adult patients, were considered for inclusion. Only English language articles were considered. We excluded review articles, case reports, and genetic studies exclusively on animal models. We omitted studies only on genetic determinants for neuropathic pain severity as well as genetic studies on cancer pain and non-neuropathic pain. Inclusion and exclusion criteria are listed in Supplementary Table S2.

Data collection

The first author (AV) performed literature searches and removed the duplicates identified in all five databases. Articles were screened using the keywords in titles and abstracts using R [65] script and verified manually to determine whether they met the above study criteria. Articles were examined and assessed independently by AV and the second author (HLH). Further, reference lists

of all screened articles were used to retrieve additional studies by hand search. Subsequently, full-text articles were retrieved and reviewed for eligibility. Any disagreements were discussed between AV and HLH. The list of excluded studies after full-text screening can be found in Supplementary Table S3. Twenty-seven articles were included from preliminary searches and then we re-ran the searches in April 2017 using the original search strategies to include any more recent studies.

Data extraction

Data extraction was performed by the first author and any clarification was discussed with last author (BHS). The quality of all included studies was evaluated according to the Strengthening the Reporting of Genetic Association study (STREGA) guidelines [43]. The quality score was calculated for each study based on the 22 key items grouped into seven categories: title and abstract, background, study selection, statistical methods, reporting outcome, statistical methods, previous supporting evidence or validation, and funding source information (see Supplementary Table S4, S5) and scores ranged from 0 (lowest) to 30 (highest). Higher scores represent higher-quality studies. The following information was extracted from all the included studies: first author, year, study type, study characteristics, genotype method, genes, genetic markers, allele frequencies, statistical model and outcomes. Information on the transcriptional and epigenetic regulation of single nucleotide polymorphisms (SNP) were obtained using the RegulomeDB [6], UCSC genome browser [61], and Haploreg [74].

Meta-analysis

We conducted meta-analyses of all the potential risk variants that were reported by more than one study on different NP conditions. We calculated odds ratios (OR) and 95% confidence intervals (CIs) using reported allele frequencies by authors. We performed fixed effect meta-analyses to determine the summary risk estimates and CIs, and assessed the heterogeneity across the studies by calculating I^2, and heterogeneity p-value from Cochrane Q test and generated forest plots using metafor R –package [72]. Publication bias was assessed using Egger's regression test for asymmetry and funnel plots were generated using metafor R-package [72].

Results

Study selection

The systematic literature searches resulted in 3461 studies after removing duplicates and non-English language articles. We did not find any additional studies through other resources. After screening titles and abstracts, 48 relevant full-text articles were assessed, of which 21 articles that did not meet the study criteria were excluded as they were treatment response studies, studies investigating genetic predictors for NP severity, or studies investigating pain-related conditions that are not considered to be NP. **Figure 1** illustrates the study selection process and reasons for full-text articles exclusion. Two studies [8,75] were identified when we updated the systematic search until April 2017. We therefore identified a total of 29 studies for inclusion in this review published between January 1999 and April 2017.

Characteristics of included studies

The characteristics of the study type, sample size, case-control ascertainment and study population are summarized in **Table 1**. Of the 29 studies, 21 were CGAS, 4 employed traditional molecular genetic methods, and 3 used GWAS on different NP conditions. The most studied NP conditions were persistent post-surgical pain (PPSP), diabetic neuropathic pain (PDPN), post-herpetic neuralgia (PHN), and sciatica. Other NP conditions, including carpal tunnel syndrome (CTS), trigeminal neuralgia (TN), and pain in multiple sclerosis (MS) patients were studied at least once (see **Figure 2**). Seventeen studies investigated NP risk in a European population, seven studies were based in an East Asian population, two studies were conducted in an American population with ad-mixed ancestry, and other studies were conducted in Israeli and South African populations. Most of the studies had a very small sample size (< 500 samples). NP case ascertainment varied across the studies: 24 studies screened the subjects based on clinical examination and/or used an assessment tool and questionnaires for pain (MRI, quantitative sensory testing, and monofilament test), 2 studies used only questionnaires (Inguinal pain, painDETECT) and 2 studies from the same cohort used a prescription history and/or clinical assessment tool. In all studies, either healthy subjects with no history of pain, or patients affected by disease of interest who did not develop neuropathic pain, were defined as controls. All included studies mainly focussed on the influence of genetic variants in the risk of developing NP and a very small number of studies examined the genetic factors for NP severity as well. **Table 2** presents the summary of genetic markers, genotype

method, and statistical modelling used in all 29 studies, study outcomes, risk alleles identified, information on HWE, effect-sizes, CIs, and p-values, if they were provided by the authors. The calculated quality score for all genetic association studies is shown in **Table 2**. The accuracy and transparency of reporting study outcomes improved from earlier studies to most recent studies (see Supplementary Figure S1).

Molecular genetics studies

Molecular genetics studies identified an association between NP and variants in three genes *(SCN9A, SCN11A,* and *MPZ)* encoding voltage-gated sodium channel and myelin zero protein, respectively. Two studies [10,25] reported an association between R1150W mutations in the *SCN9A* gene and chronic NP. Huang *et al* found eight mutations in the *SCN11A* gene in 12 unrelated individuals from a cohort of 345 subjects with painful peripheral neuropathy [32]. Ramirez et al reported an association between Trp101stop mutations (*MPZ*) in individuals affected with hereditary neuropathy and debilitating NP [55].

Genetic association studies

We identified genetic polymorphisms in or near 34 genes, of which 26 (from CGAS and GWAS) were significantly associated with NP in at least one study cohort. Eight genes that had previously been postulated as candidates, based on biological evidence, showed no statistical significance in their association with NP in our systematic review.: matrix metallopeptidase 1 (*MMP1*); cytochrome P450 Family 2 Subfamily D Member 6 (*CYP2D6*); transient receptor potential cation channel subfamily A member 1 (*TRPA1*); transient receptor potential cation channel vanilloid subfamily member 1 (*TRPV1*); transient receptor potential cation channel subfamily M member 8 *(TRPM8);* brain-derived neurotrophic factor (*BDNF*); calcium voltage-gated channel alpha2 delta 2 subunit (*CACNAD2*); and glutamate ionotropic receptor kainite type subunit 4 (*GRIK2*). Some studies reported genetic variants in human leukocyte genes (*HLA-A*, *HLA-B*, *HLA-DRB1*, and *HLA-DQB1),* catechol-O-Methyltransferase (*COMT*), opioid receptor Mu 1 (*OPRM1*), tumour necrosis factor alpha (*TNFA*), interleukin-6 (*IL6*) and GTP cyclohydrase (*GCH1)* that were significantly associated with two or more NP conditions. Amongst them, some studies showed conflicting results. However, the effect size and direction of those reporting NP associated variants were similar across the studies. We therefore conducted quantitative syntheses, where possible, for these variants to assess the level of true associations with NP. Funnel plots and p-values from

Egger's regression test for any possible reporting bias showed no evidence of publication bias (see Supplementary Figures S2-S9). However, funnel plots are limited in detecting publication bias when there are a small number of studies. All the reported genes from both CGAS and GWAS were categorized based on the function or related pathways and only genes significantly associated with NP are in bold text, **Table 3**. Of all the reported genetic variants, 75% are non-coding variants that can regulate gene expression and around 40% of these were located in an enhancer region (**Figure 3**).

Candidate gene association studies

Neurotransmission

OPRM1

The association between A118G (Asn40Asp) in *OPRM1* and the risk of developing NP has been investigated in three studies [7,29,39]. Cheng *et al* examined the association of rs1799971 with 15 painful and 50 painless diabetic foot ulcer patients and reported that patients carrying this variant were less susceptible to NP (OR, 0.24; CI, 0.07-0.80, $P=3.8\times10^{-02}$) [7]. In contrast, rs1799971 was not significantly associated with NP in individuals with PPSP (P=0.58) [29]. Kalliomaki *et al* showed no significant differences in the distribution of rs1799971 with NP in 47 Swedish subjects who had undergone hernia surgery compared with pain-free subjects (P=0.935). This study was not considered for meta-analysis because allele frequency data was not reported explicitly [39]. The conflicting results might be due to the low number of cases (n<50) and controls (n<115) used in these studies. The meta-analysis of two studies [7,29] found that rs1799971 was not significantly associated with NP, with no heterogeneity (OR, 0.55; CI, 0.27-1.11; P=0.09) (**Figure 4**).

COMT

COMT encodes catechol-O-methyltransferase and this involved in the breakdown of catecholamine neurotransmitters [45]. Five studies in our review interrogated the association of rs4680 in *COMT* with different NP conditions and reported inconsistent results. Armero *et al* were the first to investigate the association between *COMT* variant and NP, in Spanish patients with distinct NP conditions [1]. They found no significant distribution of Val158Met genotypes in NP cases compared to healthy controls (P=0.9). Similarly, another Spanish cohort of 109 subjects did not show any significant association between *COMT* and CTS [19]. However, this study reported

that CTS subjects carrying the Met/Met genotypes suffered from more pain than others. Another study from a Spanish population reported a significant association between rs4680 and NP in 58 MS patients with pain compared to 50 MS patients without pain ($P=4.6\times10^{-02}$) [20]. These conflicting results in the same population may be because they were examining NP of differing aetiology. Another cohort of 258 Norwegian subjects with sciatica did not show an association between rs4680 and NP risk (P=0.1) [35]. They found a significant association between the Met allele of *COMT*, and pain severity and demonstrated that this may contribute to the progression of NP in sciatica patients [35]. Finally, Hegarty *et al* found no significant association between *COMT* and PPSP [29]. The meta-analysis of all five studies from the European population with a total of 589 NP cases and 579 controls did not show a significant association between the Met allele of *COMT* and NP (rs4680, OR, 0.95; CI, 0.81-1.13; P=0.584) (**Figure 5**).

SCN9A

SCN9A is involved in ion channel activity. The recent study by Li *et al* found that four statistically significant variants were associated with 887 PDPN cases compared to 1029 controls (rs7449889; OR, 2.6; $P=4\times10^{-03}$, rs3750904; OR, 2.2; $P=8.96\times10^{-03}$, rs4369876; OR, 2.1; $P=4.7\times10^{-02}$, rs12478318; OR, 2.1; $P=4.7\times10^{-02}$) [42]. Genetic variants in rs4369876 and rs12478318 SNPs in *SCN9A* were also associated with pain severity.

SLC6A4

Solute carrier family 6 member 4 protein or serotonin transporter (5-HTT) protein is encoded by the *SLC6A4* gene on 17q11.2. Cui *et al* were the first to report an association between 5-HTTLPR variant near *SLC6A4* and susceptibility to TN. A significant difference in the 5-HTTLPR short-short genotype distribution was found in the 244 TN patients compared to 280 healthy controls from an East Asian ancestry (OR, 5; CI, 1.45-3.17; $P=3.4\times10^{-02}$) [9]. A significant association of the 5-HTTLPR short-short genotype with TN pain severity was also reported. This study found no association between rs25531 in *SCL6A4* and TN risk or pain severity ($P<0.05$).

CACNG2

CACNG2 encodes the transmembrane AMPAR regulatory protein (TARP) gamma-2 which modulates neuronal calcium channels [57]. Nissenbaum *et al* interrogated the association between 12 polymorphisms in *CACNG2* and pain in breast cancer subjects who had undergone breast

surgery [51]. A significant association of the A-C-C *CACNG2* haplotype (rs4820242-rs2284015-rs2284017; OR, 1.65; P=1×10-02) with susceptibility to PPSP was reported in this study, though they did not confirm that the pain was specifically neuropathic.

Immune response

***HLA* genes**

Six studies included in this review have investigated the association between polymorphisms in *HLA* genes and NP conditions including PHN and PPSP (highlighted in **Table 2**). Among these, three studies examined *HLA* frequencies in the independent cohorts of subjects with persistent pain for more than three months after the disappearance of herpes zoster (HZ) vesicular eruptions, subjects with HZ who did not develop PHN, and healthy controls. Ozawa *et al* were the first to report positive associations of the HLA-alleles, *HLA-A*33* and *HLA-B*44*, and an *HLA-DRB1*1302* haplotype with PHN in a Japanese population [53]. Sato *et al* confirmed these associations in the same population [59]. Two studies examined these associations in two independent Japanese cohorts that included HZ patients with pain and without pain as well as healthy controls [58,63]. These suggested that the risk alleles contribute to the development of PHN but are not associated with HZ. A Korean study by Chung *et al* validated the previously reported HLA risk alleles for PHN and found that *HLA-B*44* showed the strongest association with PHN though not with HZ [8]. In addition, this study reported positive associations of *HLA-B*13*, *-B*15*, *DRB1*10.01*, and *DRB1*1202* with PHN. Dominguez *et al* reported significant associations of *HLA-DRB1*04* and *HLA-DQB1*03:02* allele frequency and haplotype frequency in patients with persistent pain more than six months after surgery, compared to those without persistent pain [16]. Although there are differences in *HLA* allele typing between the studies, we combined the frequency of allele subtypes and calculated the OR and CI for meta-analysis.

The meta-analysis included all studies that found significant associations of *HLA-DRB1*13*, *HLA-DRB1*04*, *HLA-A*02*, *HLA-A*33*, *HLA-B*44*, and *HLA-DQB1*03* alleles in two subgroups: patients who developed NP after HZ or post-surgery compared with patients who did not develop NP after HZ or post-surgery; and patients who developed NP after HZ compared with healthy controls. The meta-analysis of four studies [8,53,58,63] found that NP (PHN) is associated with *HLA-DRB1*13*, *HLA-DRB1*04*, *HLA-A*02*, and *HLA-A*33* compared to healthy controls, with no or moderate heterogeneity (OR, 2.96; CI, 1.93-4.56; $P=7.9\times10^{-07}$, OR, 1.40; CI, 1.02-1.93;

P=3×10^{-02}, OR, 0.64; CI, 0.47-0.87; P=4×10^{-03}, and OR, 2.41; CI, 1.72-3.39; P=3.9×10^{-07}) (**Figure 6A,C,E,G**). The *HLA-DRB1*13* allele showed a significant association with NP (PHN, PPSP) compared to the subjects with no pain after HZ infection or after inguinal hernia surgery, with no heterogeneity (OR, 1.59; CI, 1.04-2.41; P=3.1×10^{-02}) [8,16,58,63] (**Figure 6B**). The meta-analysis of two studies [16,53] found that NP (PHN, PPSP) was associated with *HLA-DQB1*03*, with no heterogeneity (OR, 2.86; CI, 1.57-5.21; P=6×10^{-04}) (**Figure 6D**). Meta-analysis of *HLA-A*02* alleles from three studies [8,58,63] found a significant protective effect on PHN, with no heterogeneity (OR, 0.60; CI, 0.41-0.90; P=1×10^{-02}) (**Figure 6F**) and *HLA-A*33* increased the risk of developing NP compared with patients who did not develop NP after HZ (OR, 2.32; CI, 1.42-3.80; P=8×10^{-04}) (**Figure 6H**). Meta-analysis found that NP was strongly associated with *HLA-B*44* and that this allele increased the risk of developing NP compared to healthy controls as well as HZ patients without PHN (OR, 3.17; CI, 2.22-4.55; P=3.5×10^{-10} and OR, 3.50; CI, 2-6.11; P=1.8×10^{-05}), with very low heterogeneity (**Figure 6I,J**).

Cytokines

Noponen-Hietala *et al* investigated the association between 16 sequence variations in 10 pro-inflammatory cytokine genes (interleukins, tumour necrosis factor) and NP. They found a significant association between rs13306435 (T15A) in *IL6* and NP after correcting for multiple testing (rs13306435; OR, 4.4; CI, 1.2-5.7; P=1.1×10^{-02}). The associations between variants in *IL1A*, *IL1B* and *TNFA* and NP were not statistically significant after multiple correction [52]. Further haplotype analysis using 4 SNPs (rs1800797; G-597A, rs1800796; G-572C, rs1800795; G-174C, and rs13306435; T15A) in *IL6* showed a significant association with sciatica, and most notably, the GGGA haplotype was strongly associated with NP (OR, 5.4; CI, 1.5-9.2; P=3.3×10^{-03}). Stephens *et al* reported that 13 SNPs in 7 pro-inflammatory and anti-inflammatory cytokine genes (*IFNGR1*, *IL1B*, *IL2*, *IL6*, *IL8*, *IL17A*, *NFKB2*, and *TNFA*) were not significantly associated with NP after adjusting for covariates such as race, pain before surgery and pain severity after surgery [62]. They found that variants in interleukin-1 receptor 2 (*IL1R2*) (rs11674595; OR, 36.07; CI, 2.02-643.37; P=1×10^{-02}) and the CGCGATT haplotype in interleukin-10 (*IL10*) (rs3024505-rs3024496-rs1878672-rs1518111-rs1518110-rs3024491) were significantly associated with NP after adjusting for covariates (OR, 0.21; CI, 0.05-0.91; P=3×10^{-02}). Kalliomaki *et al* reported that rs1800629 in *TNFA* was significantly associated with the risk of developing NP in 47 Swedish

subjects who had undergone hernia surgery (Relative Risk,1.93; CI, 1.03-3.61; $P=3.6\times10^{-02}$) [39]. All of these studies examined different variants in *TNFA* and were consistent in reporting associations with NP.

Metabolism

GCH1

Three studies examined the association of genetic variants in *GCH1* with the risk of developing NP, in populations with different ancestries. Wadley *et al* investigated the association of *GCH1* (rs10483639, rs752688, rs4411417, rs8007201, rs3783641, and rs8007267) with NP in HIV-SN subjects of black African ethnicity [73]. They found that a 3-SNP haplotype (CAT) and a 6-SNP haplotype (CTCGAT) were associated with a lower risk of having NP ($P=2\times10^{-02}$, and $P=4\times10^{-02}$) but no single SNP showed an association with NP. Kalliomaki *et al* found no significant association of the rs8007267-rs3783641-rs10483639 haplotype in *GCH1* with NP in 47 Swedish subjects who had undergone hernia surgery [39]. Hegarty *et al* reported a significant association between the C allele of rs8007267 in *GCH1* and PPSP ($P=2\times10^{-02}$) but not with other SNPs (rs3783641, rs10483639) [29]. A meta-analysis could not be performed because not all studies provided genotype information.

Iron metabolism-related genes

Kallianpur *et al* studied the association between genetic variants in 19 iron-regulatory and iron-transport-pathway genes and distal peripheral neuropathic pain (DPN) in 168 HIV-SN subjects from an ad-mixed American population [38]. They found significant associations between DPN and seventeen variants in eight genes encoding: Aconitase 1 (*ACO1*), Beta-2-Microglobulin (*B2M*), Bone morphogenetic protein 6 (*BMP6*), Frataxin (*FXN*), Ceruloplasmin (*CP*), Transferrin (*TF*), Transferrin cell surface receptor (*TFRC*), and Solute carrier family11 member2 (*SLC11A2*). Polymorphisms (rs2026739, and rs7033149) at 9p21.1 in *ACO1* were associated with increased risk (OR, 1.5; CI, 1.1-2.0; $P=7\times10^{-03}$ and OR, 1.6; CI, 1.1-2.4; $P=1.2\times10^{-02}$) and rs4495514 in *ACO1* was associated with a decreased risk of developing NP in HIV-SN subjects (OR, 0.4; CI, 0.2-0.9; $P=3.6\times10^{-02}$). They reported that rs16966334 and rs1901531 in *B2M* (OR, 2.4; CI, 1.3-4.2; $P=3\times10^{-03}$, and OR, 1.6; CI, 1.1-2.5; $P=2.8\times10^{-02}$) and variants in *CP* increased the risk of developing NP (rs13072552; OR, 1.6; CI, 1.1-2.4; $P=7\times10^{-03}$, rs13075921; OR, 1.6; CI, 1.0-2.4; $P=4.8\times10^{-02}$, and rs3816893; OR, 1.9; CI, 1.2-3.0; $P=4\times10^{-03}$). They also found that rs270388,

rs267202, and rs267206 in *BMP6*, were significantly associated with NP (OR, 1.3; CI, 1.0-1.8; $P=5\times10^{-02}$, OR, 0.8; CI, 0.6-1.0; $P=5\times10^{-02}$, and OR, 1.4; CI, 1.0-2.0; $P=3\times10^{-02}$). An iron-related SNP, rs3793451 at 9q21 in *FXN* was significantly associated with lower risk of developing DPN (OR, 0.4; CI, 0.2-0.9; $P=4.7\times10^{-02}$). Significant associations between two SNPs in *TF* and distal NP was found in HIV-SN subjects of mixed ancestry (rs2718796; OR, 3.1; CI, 1.4-7.3; $P=7\times10^{-03}$ and rs8177306; OR, 0.4; CI, 0.2-0.9; $P=2.3\times10^{-02}$). This study also reported significant associations between the T allele of rs480760 in *TRFC* and rs224446 in *SLC11A2*, and NP (OR, 0.6; CI, 0.4-0.9; $P=4\times10^{-03}$, and OR, 0.7; CI, 0.4-1.0; $P=4.7\times10^{-02}$). They also reported associations between these SNPs and greater severity of DPN both in black and white non-Hispanic populations ($P < 5\times10^{-02}$).

Genome-wide association studies

Receptor signalling

GFRA2

The first published GWAS study on neuropathic pain performed by Meng *et al* reported suggestive significant SNPs ($P<10^{-6}$) at 8p21.3 near *GFRA2* (glial cell-line derived neurotrophic factor receptor alpha 2), which is related to the receptor signalling pathway as well as to the immune response. In this study, a total of 572 diabetes patients with NP cases, defined by their prescription history and a positive monofilament sensory test on the foot, were compared with 2491 diabetic patients without NP in the Scottish population-based GoDARTS cohort [47]. The most significant intergenic SNP, rs17428041 near *GFRA2*, showed borderline significance in association with NP (OR, 0.67; CI, 0.57-0.78; P, 1.77×10^{-7}).

PRKCA

PRKCA (protein kinase C alpha) encodes for protein kinase C alpha protein and is involved in neurotransmission and apoptosis signalling. Warner *et al* found an association between a variant, rs887797, in *PRKCA* that reached suggestive significance ($P=4.29\times10^{-06}$) and possible NP subjects who had undergone post total joint replacement. This finding was validated in two independent UK cohorts of individuals who had undergone hip or knee replacement and individuals with knee pain and screened for NP using the painDETECT questionnaire from the Rotterdam study [75]. They conducted a meta-analysis of these cohorts which showed a suggestive association of

rs887797 in *PRKCA* with NP (OR, 2.41; CI, 1.74-3.34; $P=1.29\times10^{-07}$) in the random effects recessive model.

Immune response / Ion binding

HMGB1P46 / ZSCAN20-TLR12P

A gender specific GWAS reported a suggestively significant intergenic SNP at 8q23.1 mapped to nearby *HMGB1P46* and NP in male individuals with diabetes compared with patients without NP in the Scottish population-based GoDARTS cohort (rs6986153; OR, 1.67; CI, 1.34-2.08; $P=8.02\times10^{-7}$) [46]. Meng *et al* also reported a suggestively significant intergenic SNP at 1q35.1 mapped to nearby *ZSCAN20-TLR12P* (zinc finger protein-toll-like receptor) and NP in female individuals with diabetes (rs71647933; OR, 2.31; CI, 1.68-3.17; $P=2.74\times10^{-7}$) [46].

Discussion

This systematic review has summarized 29 genetic studies in humans that have interrogated the relationship between genetic factors and the presence of different neuropathic pain conditions. All included studies in this review have defined the NP cases based on clinical examination or clinical assessment or pain questionnaire or prescription history, and controls as either healthy controls or patients without pain at the time of the study. We identified several genetic associated variants in twenty-eight genes that are involved in various biological pathways including neurotransmission, receptor signalling, immune response, iron metabolism, drug metabolism, receptor binding and ion binding. The majority of reported variants near genes overlap with enhancer or promoter histone markers, and few genes are transcription factors and targets for microRNAs. This indicates that few of these variants influence protein expression directly, and that most only indirectly influence the expression of genes. It suggests that epigenetic mechanisms may contribute to NP risk. However, the majority of the included studies had small sample sizes and lacked validation. One potential limitation of all included studies in this review was the employment of varying case definitions, and uncertain control ascertainment, irrespective of different NP conditions. Very few studies addressed the exclusion of controls based on co-morbidities related to any pain. Moreover, few candidate gene association studies tested the association of variants using a model without multiple adjustments. Most importantly, only a small number of studies have adjusted the association model with either more general covariates such as age, gender, smoking, and BMI or

with study-specific covariates such as pain severity, ethnicity, surgery type and therapy. Some studies had not reported summary statistics in detail. The GWAS in this field are few and have failed to replicate previously reported genes, perhaps due to small sample size or differences in case definition. In future studies, these limitations need to be considered and resolved.

Traditional molecular genetics studies found gain-of-function mutations in *SCN9A, SCN11A,* and Trp101stop mutations in NP patients compared to the healthy controls. *SCN9A* and *SCN11A* are mainly expressed in nociceptive sensory neurons of the dorsal roots and play an important role in regulating pain signals [2,56]. Evidence suggests that the sodium channel genes, *Na_v 1.9* and *Na_v 1.7* could be used as molecular targets for treating NP [18]. The most significant association between non-synonymous variant (rs3750904) in *SCN9A* and NP in diabetes patients has been confirmed in a genetic association study [42]. Moreover, these studies have identified potential candidate genes for future association studies. *MPZ* was only identified in a single study with a specific NP condition, and conclusions must be limited. To date, three GWA studies on different NP conditions (PDPN and PPSP) have identified suggestive signals ($P<5\times10^{-06}$) at chr8p21.3, chr1p35.1, chr8p23.1, and chr17q24.2 loci, in discovery cohorts from the European population, and the association of chr17q24.2 (*PRKCA*) with NP was confirmed in an independent cohort of subjects with knee or hip replacement surgery. Other loci, chr8p21.3, chr1p35.1, and chr8p23.1, associated with NP in a diabetes population, have not been confirmed in replication cohorts, and this may be because of differences in case definition or lack of appropriate sample sizes. Of the CGAS reviewed in this study, variants within *SCN9A, IL10, IL1R2, B2M, BMP6, TF, CP, TFRC, ACO1, FXN, SLC6A4,* and *CACNG2* were only interrogated in single studies and significantly associated with NP but this needs to be validated in larger sample sizes. Genetic variants in *COMT*, *HLA* genes, *OPRM1, GCH1, IL6* and *TNFA* were investigated their association with NP in more than one study.

The most extensively studied candidate variant is A118G in exon 1 of *OPRM1* in several pain conditions; this has been found to be associated with lower pain levels and is mainly involved in neurotransmission pathways. This missense variant at 6q25.2 results in an amino-acid substitution (Asn40Asp) which may increase the binding affinity of β-endorphin. Meta-analysis of two studies found no significant association between rs1799971 in *OPRM1* and NP. However, replication cohorts with larger sample sizes are necessary to validate these findings. A systematic review and

meta-analysis study has reported that individuals carrying the Met allele of *COMT* are more susceptible to other types of chronic pain and to severity of pain [64]. Our meta-analysis results found that *COMT* was not significantly associated with NP; although one study reported a significant association with NP in MS patients, other studies reported non-significant associations with sciatica, PHN, and PPSP. Further studies with larger sample size and consistent case and control definitions may reveal the true association of *COMT* variants with NP.

Evidence suggests that polymorphisms in *GCH1* decrease pain levels by altering the expression of this enzyme [44,66]. One study found a positive association between an intronic variant, rs8007267, in *GCH1* and PPSP. Two studies investigated the association of *GCH1* haplotypes (rs752688, rs3783641, rs8007201) with NP and reported inconsistent results. Larger cohort studies might validate the association of rs8007267 with NP, confirm the haplotypes association, and identify more NP susceptibility variants in *GCH1*.

The *HLA* gene complex is a highly polymorphic region located on the short arm of chromosome 6 and comprises more than 200 genes. Association between *HLA* genes and NP in herpes zoster patients (PHN) are the most studied in the East Asian population and one study investigated this relationship in a European population. Our fixed effect meta-analyses result found that polymorphisms in *HLA-DRB1*13*, *HLA-DRB1*04*, *HLA-DQB1*03*, *HLA-A*33*, and *HLA-B*44* showed significant increases in the risk of having NP and effect sizes and direction were consistent across the studies. In contrast, *HLA-A*02*, a protective allele, conferred reduced risk for NP. Only moderate heterogeneity was observed in *HLA-DRB1*04* and *HLA-A*02* combined analyses due to different ethnicity. Apart from *HLA* genes, cytokines such as *IL6* and *TNFA* have been shown to be linked to several chronic pain conditions [40] and variants in *TNF* haplotypes have been shown to be associated with pain severity in HIV-SN patients of South African ancestry [30]. Interestingly, activation of immune cells and then overexpression of pro-inflammatory cytokines has been seen in neuropathic pain patients [3,69].Our review also found two studies that examined the contribution of several variants in inflammatory cytokine genes to the risk of developing NP and found that *IL6*, *IL10*, *IL1R2*, and *TNFA* were significantly associated with NP but these studies explored different variants in these genes and were limited by study sample size. Therefore, we could not combine these studies to assess their true association with NP susceptibility. However, large-scale studies would reveal the relationship between inflammatory response and its role in the

pathophysiology of NP. These studies demonstrate that further investigation of polymorphisms in *HLA* genes and inflammatory genes could identify potential genetic variants which could be used as drug targets for NP to modulate the immune responses.

~~**Limitations of the included studies**~~

Strengths and limitations of this review

To our knowledge, this systematic review is the first to date summarizing the genetic factors that contribute to the risk of developing NP in humans. Recent reviews focussed on the risk factors, including genetic factors, for specific conditions including PDPN and PHN [21,26]. Strengths of this review include the literature search for articles reporting molecular genetic findings and genetic association studies in five databases, applying a standard study design according to PRISMA guidelines, employing explicit search terms using previously validated keywords, utilizing text mining methods to filter studies based on appropriate inclusion and exclusion criteria, updating recent records using original search strategies, and employing data synthesis of all eligible genetic association studies. We employed standard meta-analysis study design and reporting methods according to STREGA quality guidelines for genetic association studies.

This review excluded non-English language articles and may therefore have missed any important new findings reported in other languages. Our meta-analyses results were limited by the small sample sizes of relatively few eligible studies and this may affect the robustness of the results. For example, heterogeneity is difficult to estimate when studies are few in number [23,31]. A few included studies in this review explored the association of SNPs with NP as well as pain severity; this review focussed only on genetic factors for the risk of developing NP and may not have captured neuropathic pain severity associated genetic variants. These variants may be involved in NP susceptibility as well, and we may have missed them. Our included studies examined genetic factors associated with NP in studies that reported both human and experimental animal models as well but we have not considered results from animal model studies alone. The translation of animal model studies to human is still under debate, especially in this field. Finally, a few included studies from the same research group may overlap with each other.

Recommendations for future research

Our systematic review highlights the current knowledge of genetic factors that influence the risk of having NP and reveals recommendations for future studies. Our review lists potential candidate genes which can be validated in further studies with large sample sizes from different ethnic groups. In addition, future haplotype analysis could reveal the true association of haplotype blocks in candidate genes with NP susceptibility. A large-scale GWAS with consensus NP phenotype in independent cohorts could shed light on other potential genetic polymorphisms across the genome associated with NP susceptibility or protection. Pathway analysis could explore additional genes involved in the immune response, neurotransmission and metabolism pathways which would be useful to identify multiple genes in pathways that contribute to NP susceptibility. In addition, exome sequencing might identify common and rare causal variants associated with NP risk.

Conclusions

This systematic review gathered all genetic studies in humans and identified several variants in or near twenty-eight genes significantly associated with NP. Our meta-analysis results suggest that variants in *HLA-DRB1*13*, *HLA-DRB1*04*, *HLA-DQB1*03*, *HLA-A*33*, and *HLA-B*44* increase the risk of developing NP, whereas variants in *HLA-A*02* decrease the risk and variants in *COMT*, and *OPRM1* were not associated with NP. However, larger cohort studies are necessary to validate these findings, and these could identify biomarkers for clinical prognosis and drug targeting. The limited number of case-control GWAS on NP highlights the need for large-scale GWAS with a consistent case definition. Our review suggests that multiple genetic risk factors from distinct pathways influence NP susceptibility, and their interactions may elucidate the genetic mechanisms underlying NP.

Supplementary data

Acknowledgements

This work was supported by the DOLORisk consortium which is funded by the European Union's Horizon 2020 research and innovation programme under grant agreement No: 633491. B.H.S. is a member of the DOLORisk consortium and is partly supported by this grant. He has received, on behalf of his institution, occasional lecture and consultancy fees from Pfizer Ltd, Napp Pharmaceuticals, Grunenthal and Eli Lilly. C.N.A.P is also partly supported by DOLORisk as well

as by the National Institute of Health Research (UK). H.L.H. and A.V. are supported by DOLORisk. W.M declares no conflict of interest.

References

[1] Armero P, Muriel C, Santos J, Sanchez-Montero FJ, Rodriguez RE, Gonzalez-Sarmiento R. COMT (Val158Met) polymorphism is not associated to neuropathic pain in a Spanish population. Eur. J. Pain 2005;9:229–232.

[2] Bagal SK, Chapman ML, Marron BE, Prime R, Storer RI, Swain NA. Recent progress in sodium channel modulators for pain. Bioorg. Med. Chem. Lett. 2014;24:3690–3699.

[3] Banati RB, Cagnin a, Brooks DJ, Gunn RN, Myers R, Jones T, Birch R, Anand P. Long-term trans-synaptic glial responses in the human thalamus after peripheral nerve injury. Neuroreport 2001;12:3439–3442.

[4] Bouhassira D, Lante M, Attal N, Laurent B, Touboul C. Prevalence of chronic pain with neuropathic characteristics in the general population. Pain 2008;136:380–387.

[5] Bouhassira D, Letanoux M, Hartemann A. Chronic Pain with Neuropathic Characteristics in Diabetic Patients : A French Cross-Sectional Study. PLoS One 2013;8:1–9.

[6] Boyle AP, Hong EL, Hariharan M, Cheng Y, Schaub M a., Kasowski M, Karczewski KJ, Park J, Hitz BC, Weng S, Cherry JM, Snyder M. Annotation of functional variation in personal genomes using RegulomeDB. Genome Res. 2012;22:1790–1797.

[7] Cheng KI, Lin SR, Chang LL, Wang JY, Lai CS. Association of the functional A118G polymorphism of OPRM1 in diabetic patients with foot ulcer pain. J Diabetes Complicat. 2010;24:102–108.

[8] Chung HY, Song EY, Yoon JA, Suh DH, Lee SC, Kim YC, Park MH. Association of human leukocyte antigen with postherpetic neuralgia in Koreans. Apmis 2016;124:865–871.

[9] Cui W, Yu X, Zhang H. The serotonin transporter gene polymorphism is associated with the susceptibility and the pain severity in Idiopathic Trigeminal Neuralgia patients. J. Headache Pain 2014;15:42.

[10] Dabby R, Sadeh M, Gilad R, Lampl Y, Cohen S, Inbar S, Leshinsky-Silver E. Chronic non-paroxysmal neuropathic pain - Novel phenotype of mutation in the sodium channel SCN9A gene. J. Neurol. Sci. 2011;301:90–92.

[11] Davies M, Williams R, Brophy S, Taylor A. The Prevalence , Severity , and Impact of Painful Diabetic Peripheral Neuropathy in Type 2 Diabetes. Diabetes Care 2006;29:1518–1522.

[12] Devor M, Canho S del, Raber P. Heritability of symptoms in the neuroma model of neuropathic pain: Replication and complementation analysis. Pain 2005;116:294–301.

[13] Devor M, Raber P. Heritability of symptoms in an experimental model of neuropathic pain. Pain 1990;42:51–67.

[14] Dib-Hajj SD, Rush AM, Cummins TR, Hisama FM, Novella S, Tyrrell L, Marshall L, Waxman SG. Gain-of-function mutation in Nav1.7 in familial erythromelalgia induces bursting of sensory neurons. Brain 2005;128:1847–1854.

[15] Dobrota VD, Hrabac P, Skegro D, Smiljanic R, Dobrota S, Prkacin I, Brkljacic N, Peros K, Tomic M, Lukinovic-skudar V, Kes VB. The impact of neuropathic pain and other comorbidities on the quality of life in patients with diabetes. Health Qual. Life Outcomes 2014;12:1–8.

[16] Dominguez CA, Kalliomaki M, Gunnarsson U, Moen A, Sandblom G, Kockum I, Lavant E, Olsson T, Nyberg F, Rygh LJ, Roe C, Gjerstad J, Gordh T, Piehl F. The DQB1*03:02 HLA haplotype is associated with increased risk of chronic pain after inguinal hernia surgery and lumbar disc herniation. Pain 2013;154:427–433.

[17] Duan G, Guo S, Zhang Y, Ying Y, Huang P, Wang Q, Zhang L, Zhang X. The Effect of SCN9A Variation on Basal Pain Sensitivity in the General Population: An Experimental Study in Young Women. J. pain 2015;16:971–980.

[18] Emery EC, Luiz AP, Wood JN. Nav1.7 and other voltage-gated sodium channels as drug targets for pain relief. Expert Opin. Ther. Targets 2016;29:975–983.

[19] Fernandez-de-las-Penas C, Ambite-Quesada S, Ortega-Santiago R, Martinez-Perez A, Diaz HF, Martinez-Martin J, Parejam J a. Catechol-O-methyltransferase val158met polymorphism is associated with pain and disability, but not widespread pressure pain sensitivity, in women with carpal tunnel syndrome. Pain Physician 2013;16:E591–E600.

[20] Fernández-de-las Peñas C, Ambite-Quesada S, Ortíz-Gutiérrez R, Ortega-Santiago R, Gil-Crujera A, Caminero AB. Catechol-O-methyltransferase val158met polymorphism (rs4680) Is associated with pain in multiple sclerosis. J. Pain 2013;14:1719–1723.

[21] Forbes HJ, Thomas SL, Smeeth L, Clayton T, Farmer R, Bhaskaran K. A systematic review and meta-analysis of risk factors for postherpetic neuralgia. Pain 2016;157:30–54.

[22] Freynhagen R, Baron R. The Evaluation of Neuropathic Components in Low Back Pain. Curr. Pain Headache Reports 2009 2009;13:185–190.

[23] Friede T, Röver C, Wandel S, Neuenschwander B. Meta-analysis of few small studies in orphan diseases. Res. Synth. Methods 2017;8:79–91.

[24] Gauthier A, Breuer J, Carrington D, Martin M, Remy V. Epidemiology and cost of herpes zoster and post-herpetic neuralgia in the United Kingdom. Epidemiol. Infect. 2009;137:38–47.

[25] Harrer JU, Üçeyler N, Doppler K, Fischer TZ, Dib-Hajj SD, Waxman SG, Sommer C. Neuropathic pain in two-generation twins carrying the sodium channel Nav1.7 functional variant R1150W. Pain 2014;155:2199–2203.

[26] Hébert HL, Veluchamy A, Torrance N, Smith BH. Risk factors for neuropathic pain in diabetes mellitus. Pain 2017;158:560–568.

[27] Hecke O Van, Austin SK, Khan RA, Smith BH, Torrance N. Neuropathic pain in the general population: A systematic review of epidemiological studies. Pain 2014;155:654–

662.

[28] Hecke O Van, Kamerman PR, Attal N, Baron R, Bjornsdottir G, Bennett DL, Bennett MI, Bouhassira D, Diatchenko L, Freeman R, Freynhagen R, Haanpaa M, Jensen TS, Raja SN, Rice AS, Selzter Z, Thorgeirsson TE, Yarnitsky D, Smith BH. Neuropathic pain phenotyping by international consensus (NeuroPPIC) for genetic studies : a NeuPSIG systematic review , Delphi survey , and expert panel recommendations. Pain 2015;156:2337–2353.

[29] Hegarty D, Shorten G. Multivariate prognostic modeling of persistent pain following lumbar discectomy. Pain Physician 2012;15:421–434.

[30] Hendry LM, Wadley AL, Cherry CL, Price P, Lombard Z, Kamerman PR. TNF Block Gene Variants Associate With Pain Intensity in Black Southern Africans With HIV-associated Sensory Neuropathy. Clin. J. Pain 2016;32:45–50.

[31] von Hippel PT. The heterogeneity statistic I2 can be biased in small meta-analyses. BMC Med. Res. Methodol. 2015;15:35.

[32] Huang J, Han C, Estacion M, Vasylyev D, Hoeijmakers JGJ, Gerrits MM, Tyrrell L, Lauria G, Faber CG, Dib-Hajj SD, Merkies ISJ, Waxman SG, Group PS. Gain-of-function mutations in sodium channel Na(v)1.9 in painful neuropathy. Brain 2014;137:1627–1642.

[33] Indo Y, Tsuruta M, Hayashinda Y, Karim M., Ohta K, Kawano T, Mitsubuchi H, Tonoki H, Awaya Y, Matsuda I. Mutations in the TRKA/NGF receptor gene in patients with congenital insensitivity to pain with anhidrosis. Nat. Genet. Lett. 1996;13:485–488.

[34] Inoue S, Taguchi T, Yamashita T, Nakamura M, Ushida T. The prevalence and impact of chronic neuropathic pain on daily and social life : A nationwide study in a Japanese population. Eur. J. Pain 2017;21:727–737.

[35] Jacobsen LM, Schistad EI, Storesund A, Pedersen LM, Rygh LJ, Roe C, Gjerstad J. The COMT rs4680 Met allele contributes to long-lasting low back pain, sciatica and disability after lumbar disc herniation. Eur J Pain 2012;16:1064–1069.

[36] Johansen A, Romundstad L, Nielsen CS, Schirmer H, Stubhaug A. Persistent postsurgical pain in a general population : Prevalence and predictors in the Tromsø study. Pain 2012;153:1390–1396.

[37] Johnson RW, Bouhassira D, Kassianos G, Leplège A, Schmader KE, Weinke T. The impact of herpes zoster and post-herpetic neuralgia on quality-of-life. BMC Med. 2010;8:1–13.

[38] Kallianpur AR, Jia P, Ellis RJ, Zhao Z, Bloss C, Wen W, Marra CM, Hulgan T, Simpson DM, Morgello S, McArthur JC, Clifford DB, Collier AC, Gelman BB, McCutchan JA, Franklin D, Samuels DC, Rosario D, Holzinger E, Murdock DG, Letendre S, Grant I. Genetic variation in iron metabolism is associated with neuropathic pain and pain severity in HIV-infected patients on antiretroviral therapy. PLoS One 2014;9.

[39] Kalliomäki ML, Sandblom G, Hallberg M, Grönbladh A, Gunnarsson U, Gordh T, Ginya H, Nyberg F. Genetic susceptibility to postherniotomy pain. The influence of polymorphisms in the Mu opioid receptor, TNF-α, GRIK3, GCH1, BDNF and

CACNA2D2 genes. Scand. J. Pain 2016;12:1–6.

[40] Karppinen J, Daavittila I, Noponen N, Haapea M, Taimela S, Vanharanta H, Ala-Kokko L, Mannikko M. Is the interleukin-6 haplotype a prognostic factor for sciatica? Eur J Pain 2008;12:1018–1025.

[41] Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain : risk factors and prevention. Lancet 2006;367:1618–25.

[42] Li QS, Cheng P, Favis R, Wickenden A, Romano G, Wang H. SCN9A variants may be implicated in neuropathic pain associated with diabetic peripheral neuropathy and pain severity. Clin J Pain 2015;31:976–982.

[43] Little J, Higgins JPT, Ioannidis JPA, Moher D, Gagnon F, Elm E Von, Khoury MJ, Cohen B, Jeremy GD, Paul G, Marta S, Williamson RE, Yong G, Kim Z, Candice H, Valerie YJ, Miriam T, Golding J, Duijn C Van, Mclaughlin J, Paterson A, Wells G, Fortier I, Freedman M, Zecevic M, King R, Alex CI, Nick S, Birkett VTÁMWÁN. Strengthening the reporting of genetic association studies (STREGA): an extension of the STROBE Statement. Hum Genet 2009;125:131–151.

[44] Lötsch J, Belfer I, Kirchhof A, Mishra BK, Max MB, Doehring A, Costigan M, Woolf CJ, Geisslinger G, Tegeder I. Reliable screening for a pain-protective haplotype in the GTP cyclohydrolase 1 gene (GCH1) through the use of 3 or fewer single nucleotide polymorphisms. Clin. Chem. 2007;53:1010–1015.

[45] Lundstrom K, Salminen M, Jalanko A, Savolainen R, Ulmanen I. Cloning and characterization of human placental catechol-O-methyltransferase cDNA. DNA Cell Biol 1991;10:181–189.

[46] Meng W, Deshmukh H., Donnelly LA, Torrance N, Colhoun HM, Palmer CNA, Smith BH. A Genome-wide Association Study Provides Evidence of Sex-specific Involvement of Chr1p35.1 (ZSCAN20-TLR12P) and Chr8p23.1 (HMGB1P46) With Diabetic Neuropathic Pain. EBioMedicine 2015;2:1386–1393.

[47] Meng W, Deshmukh H, Donnelly LA, van Zuydam NR, Liu Y, Zhou K, Morris AD, Colhoun HM, Palmer CNA, Smith BH. A genome-wide association study suggests an association of Chr8p21.3 (GFRA2) with diabetic neuropathic pain. Eur. J. Pain 2015;19:392–399.

[48] Merskey H, Bogduk N. Classification of Chronic Pain. 1994 p.

[49] Moher D, Liberati A, Tetzlaff J, Altman DG&, PrismaGroup. Preferred Reporting Items for Systematic Reviews and Meta-Analyses : The PRISMA Statement. PLoS Med. 2009;6:1–6.

[50] Momi SK, Fabiane SM, Lachance G, Livshits G, Williams FMK. Neuropathic pain as part of chronic widespread pain: environmental and genetic influences. Pain 2015;156:2100–2106.

[51] Nissenbaum J, Devor M, Seltzer Z, Gebauer M, Michaelis M, Tal M, Dorfman R, Abitbul-yarkoni M, Lu Y, Elahipanah T, Minert A, Fried K, Persson A, Darvasi A. Susceptibility to chronic pain following nerve injury is genetically affected by CACNG2

Susceptibility to chronic pain following nerve injury is genetically affected by CACNG2. Genome Res. 2010;20:1180–1190.

[52] Noponen-Hietala N, Virtanen I, Karttunen R, Schwenke S, Jakkula E, Li H, Merikivi R, Barral S, Ott J, Karppinen J, Ala-Kokko L. Genetic variations in IL6 associate with intervertebral disc disease characterized by sciatica. Pain 2005;114:186–194.

[53] Ozawa A, Sasao Y, Iwashita K, Miyahara M, Sugai J, Iizuka M, Kawakubo Y, Ohkido M, Naruse T, Anzai T, Takashige N, Ando A, Inoko H. HLA-A33 and -B44 and susceptibility to postherpetic neuralgia (PHN). Tissue Antigens 1999;53:263–268.

[54] Park SY, An HS, Moon SH, Lee HM, Suh SW, Chen D, Jeon JH. Neuropathic Pain Components in Patients with Lumbar Spinal Stenosis. Yonsei Med J 2015;56:1044–1050.

[55] Ramirez JD, Barnes PRJ, Mills KR, Bennett DLH. Intermediate Charcot-Marie-Tooth disease due to a novel Trp101Stop myelin protein zero mutation associated with debilitating neuropathic pain. Pain 2012;153:1763–1768.

[56] Rogers M, Tang L, Madge DJ, Stevens EB. The role of sodium channels in neuropathic pain. Cell Dev. Biol. 2006;17:571–581.

[57] Sandoval A, Arikkath J, Monjaraz E, Campbell KP, Felix R. Gamma1-dependent down-regulation of recombinant voltage-gated Ca2+ channels. Cell. Mol. Neurobiol. 2007;27:901–908.

[58] Sato-Takeda M, Ihn H, Ohashi J, Tsuchiya N, Satake M, Arita H, Tamaki K, Hanaoka K, Tokunaga K, Yabe T. The human histocompatibility leukocyte antigen (HLA) haplotype is associated with the onset of postherpetic neuralgia after herpes zoster. Pain 2004;110:329–336.

[59] Sato M, Ohashi J, Tsuchiya N, Kashiwase K, Ishikawa Y, Arita H, Hanaoka K, Tokunaga K, Yabe T. Association of HLA-A*3303-B*4403-DRB1*1302 haplotype, but not of TNFA promoter and NKp30 polymorphism, with postherpetic neuralgia (PHN) in the Japanese population. Genes Immun. 2002;3:477–481.

[60] Smith BH, Torrance N. Epidemiology of Neuropathic Pain and Its Impact on Quality of Life. Curr. Pain Headache Rep 2012;16:191–198.

[61] Speir ML, Zweig AS, Rosenbloom KR, Raney BJ, Paten B, Nejad P, Lee BT, Learned K, Karolchik D, Hinrichs AS, Heitner S, Harte RA, Haeussler M, Guruvadoo L, Fujita PA, Eisenhart C, Diekhans M, Clawson H, Casper J, Barber GP, Haussler D, Kuhn RM, Kent WJ. The UCSC Genome Browser database: 2016 update. Nucleic Acids Res. 2015;44:D717–D725.

[62] Stephens K, Cooper B a, West C, Paul SM, Christina R, Merriman JD, Dhruva A, Kober KM, Langford DJ, Luce J a, Schmidt BL, Abrams GM, Elboim C, Hamolsky D, Levine JD, Miaskowski C, Aouizerat BE. Associations between cytokine gene variations and severe persistent breast pain in women following breast cancer surgery. J Pain 2014;15:169–180.

[63] Sumiyama D, Kikkawa EF, Kita YF, Shinagawa H, Mabuchi T, Ozawa A, Inoko H. HLA alleles are associated with postherpetic neuralgia but not with herpes zoster. Tokai J. Exp.

Clin. Med. 2008;33:150–153.

[64] Tammimäki A, Männistö PT. Catechol-O-methyltransferase gene polymorphism and chronic human pain: a systematic review and meta-analysis. Pharmacogenet. Genomics 2012;22:673–91.

[65] Team RC. R: A language and environment for statistical computing. R Found. Stat. Comput. Vienna, Austria. 2014.

[66] Tegeder I, Costigan M, Griffin RS, Abele A, Belfer I, Schmidt H, Ehnert C, Nejim J, Marian C, Scholz J, Wu T, Allchorne A, Diatchenko L, Binshtok AM, Goldman D, Adolph J, Sama S, Atlas SJ, Carlezon WA, Parsegian A, Lotsch J, Fillingim RB, Maixner W, Geisslinger G, Max MB, Woolf CJ. GTP cyclohydrolase and tetrahydrobiopterin regulate pain sensitivity and persistence. Nat. Med. 2006;12:1269–1277.

[67] Toth C, Lander J, Wiebe S. The prevalence and impact of chronic pain with neuropathic pain symptoms in the general population. Pain Med. 2009;10:918–929.

[68] Treede RD, Jensen TS, Campbell JN, Cruccu G, Dostrovsky JO, Griffin JW, Hansson P, Hughes R, Nurmikko T, Serra J. Neuropathic pain: Redefinition and a grading system for clinical and research purposes. Neurology 2008;70:1630–1635.

[69] Del Valle L, Schwartzman RJ, Alexander G. Spinal cord histopathological alterations in a patient with longstanding complex regional pain syndrome. Brain. Behav. Immun. 2009;23:85–91.

[70] Vandenkerkhof EG, Mann EG, Torrance N, Smith BH, Johnson A, Gilron I. An Epidemiological Study of Neuropathic Pain Symptoms in Canadian Adults. Pain Res. Manag. 2016;2016.

[71] Veluchamy A, Hébert HL, Meng W, Palmer CNA, Smith BH. A systematic review of genetic risk factors for neuropathic pain. PROSPERO 2016:Available from http://www.crd.york.ac.uk/PROSPERO/.

[72] Viechtbauer W. Conducting Meta-Analyses in R with the metafor Package. J. Stat. Softw. 2010;36:1–48.

[73] Wadley AL, Lombard Z, Cherry CL, Price P, Kamerman PR. Analysis of a Previously Identified “Pain-Protective” Haplotype and Individual Polymorphisms in the GCH1 Gene in Africans With HIV-Associated Sensory Neuropathy. JAIDS J. Acquir. Immune Defic. Syndr. 2012;60:20–23.

[74] Ward LD, Kellis M. HaploReg: A resource for exploring chromatin states, conservation, and regulatory motif alterations within sets of genetically linked variants. Nucleic Acids Res. 2012;40:1–5.

[75] Warner SC, van Meurs JB, Schiphof D, Bierma-Zeinstra SM, Hofman A, Uitterlinden AG, Richardson H, Jenkins W, Doherty M, Valdes AM. Genome-wide association scan of neuropathic pain symptoms post total joint replacement highlights a variant in the protein-kinase C gene. Eur. J. Hum. Genet. 2017;44:1–6.

[76] Wijck AJM Van, Opstelten W, Moons KGM, Essen GA Van, Stolker RJ, Kalkman CJ,

Verheij TJM. The PINE study of epidural steroids and local anaesthetics to prevent postherpetic neuralgia : a randomised controlled trial. Lancet 2006;367:219–224.

[77] Wu M-T, Huang P-Y, Yen C-T, Chen C-C, Lee M-J. A Novel SCN9A Mutation Responsible for Primary Erythromelalgia and Is Resistant to the Treatment of Sodium Channel Blockers. PLoS One 2013;8.

Figure Legends

Figure 1. PRISMA flow diagram represents the systematic literature search and assessment process.

Figure 2. The number of published genetic studies on different neuropathic pain conditions included in this review.

Figure 3. Genomic features of all reported SNPs (in %) that are associated with neuropathic pain.

Figure 4. Forest plots of studies reporting the associations between rs1799971 in *OPRM1* and neuropathic pain either in diabetic patients or patients who had undergone surgery. Effect allele is G.

Figure 5. Forest plots of studies reporting the associations between rs4680 in *COMT* and distinct neuropathic pain conditions including surgery, sympathetic reflex dystrophy, causalgia, phantom limb, multiple sclerosis, postherpetic neuralgia, peripheral neuralgia, carpal tunnel syndrome, and central neuralgia. Effect allele is A.

Figure 6. Forest plots of studies reporting the associations between polymorphisms in *HLA* genes and neuropathic pain (NP) either in herpes zoster patients or patients who had undergone surgery. Sub grouped by the association results from patients with NP vs. without pain and patients with NP vs. healthy controls. A) *HLA-DRB1*13* allele frequencies in patients with NP vs. healthy controls. B) *HLA-DRB1*13* allele frequencies in patients with NP vs. without pain. C) *HLA-DRB1*04* allele frequencies in patients with NP vs. healthy controls. D) *HLA-DQB1*03* allele frequencies in patients with NP vs. without pain/healthy controls. E) *HLA-A*02* allele frequencies in patients with NP vs. healthy controls. F) *HLA-A*02* allele frequencies in patients with NP vs. without pain. G) *HLA-A*33* allele frequencies in patients with NP vs. healthy controls. H) *HLA-A*33* allele frequencies in patients with NP vs. without pain. I) *HLA-B*44* allele frequencies in patients with NP vs. healthy controls. J) *HLA-B*44* allele frequencies in patients with NP vs. without pain.

Figure 1

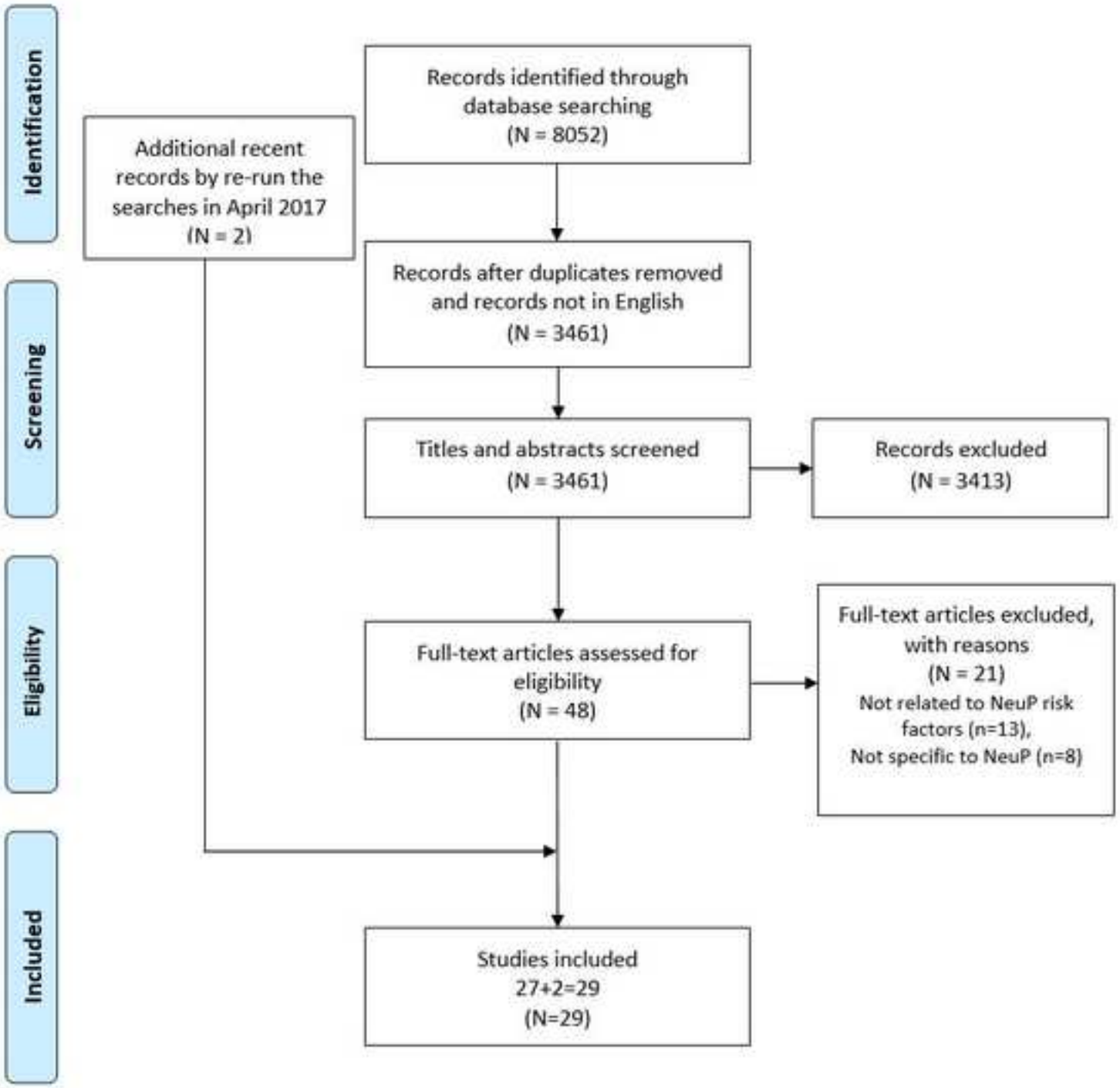


Figure 2

Click here to download Figure Figure2_2D_includedstudies_NeuPconditions.JPG

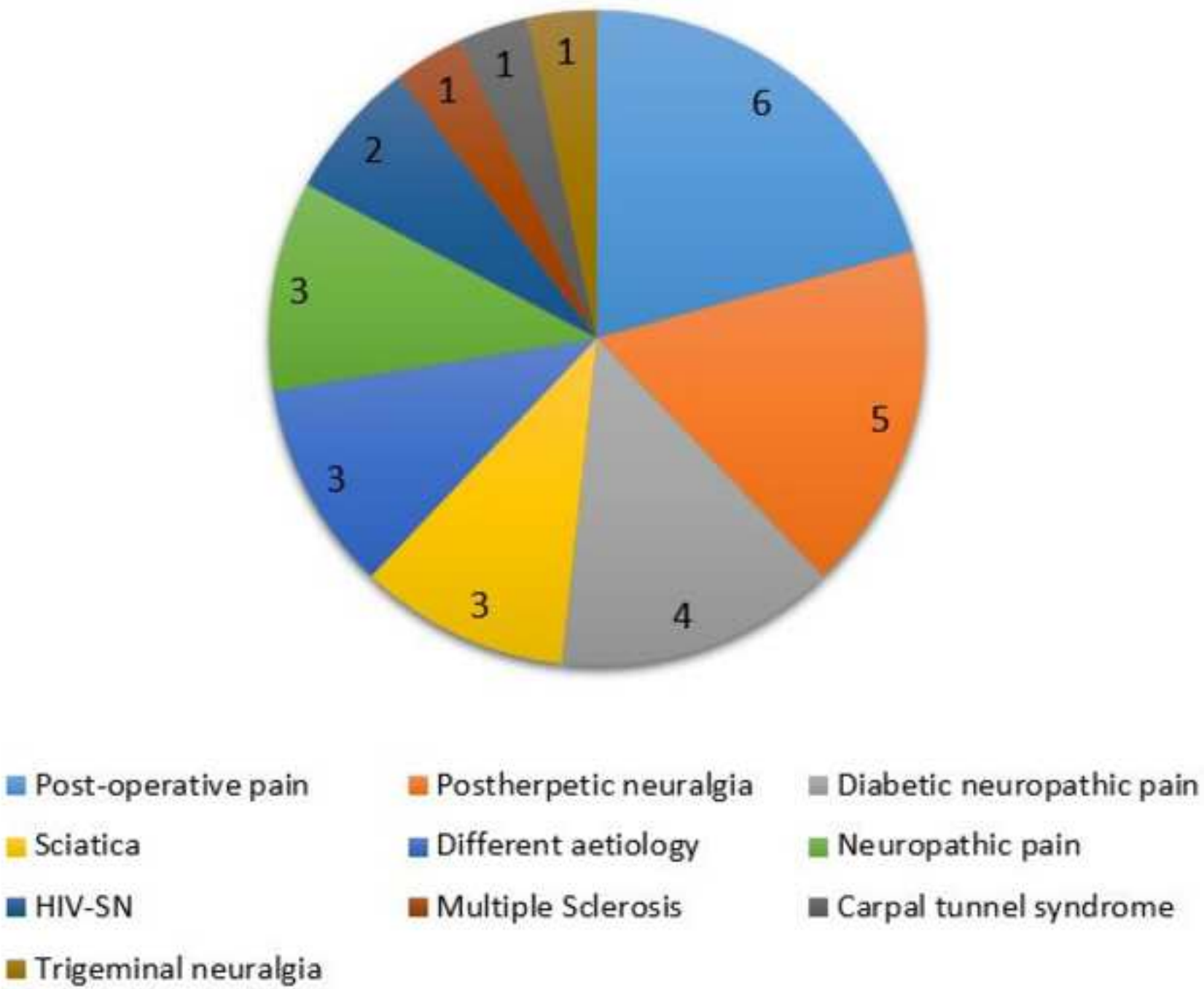


Figure 3

Click here to download Figure Figure3_geneticvariants_region.jpg

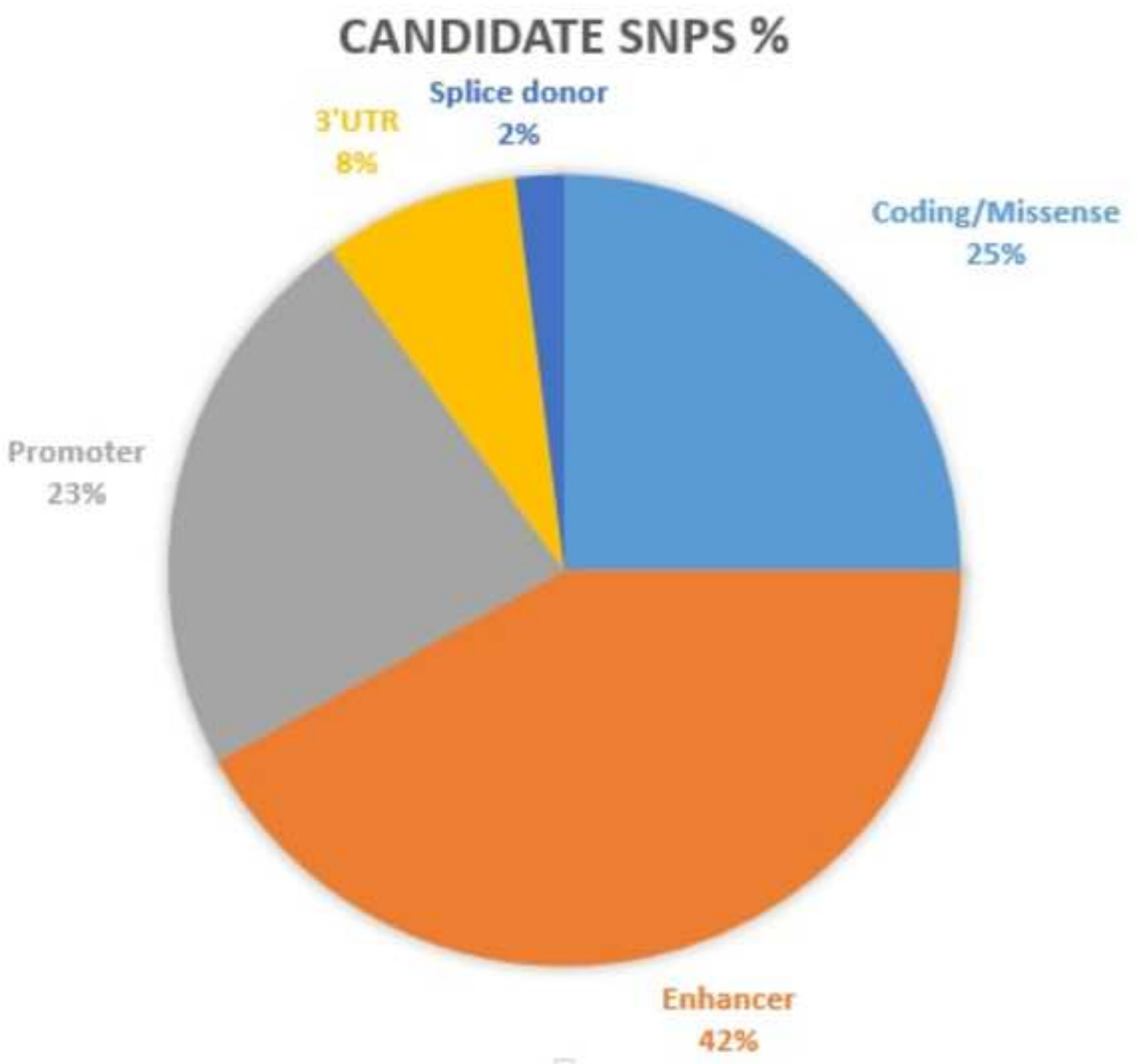


Figure 4

Click here to download Figure Figure4_OPRM1_forestplots.jpg

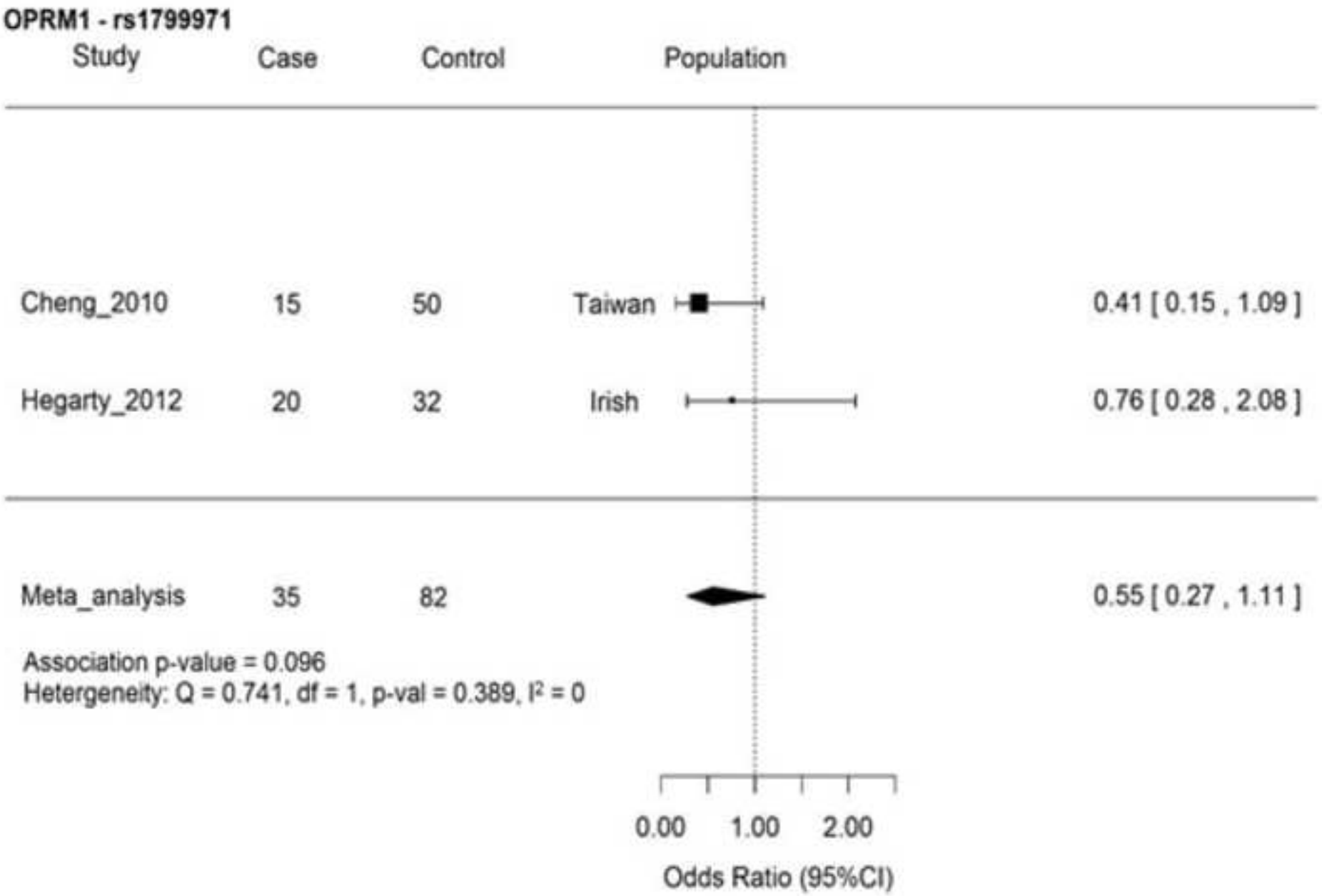


Figure 5

Click here to download Figure Figure5_COMT_Forestplots.jpg

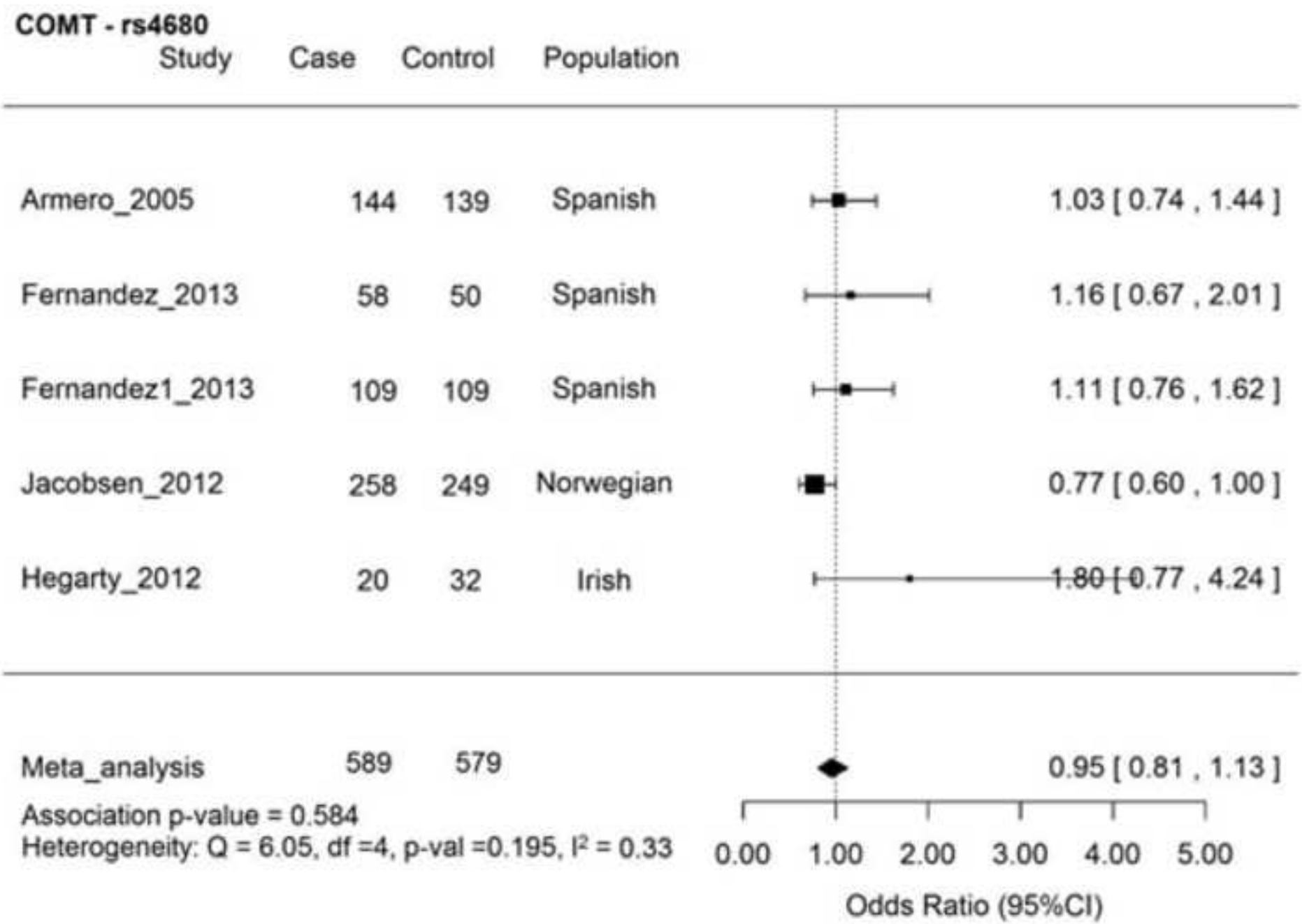
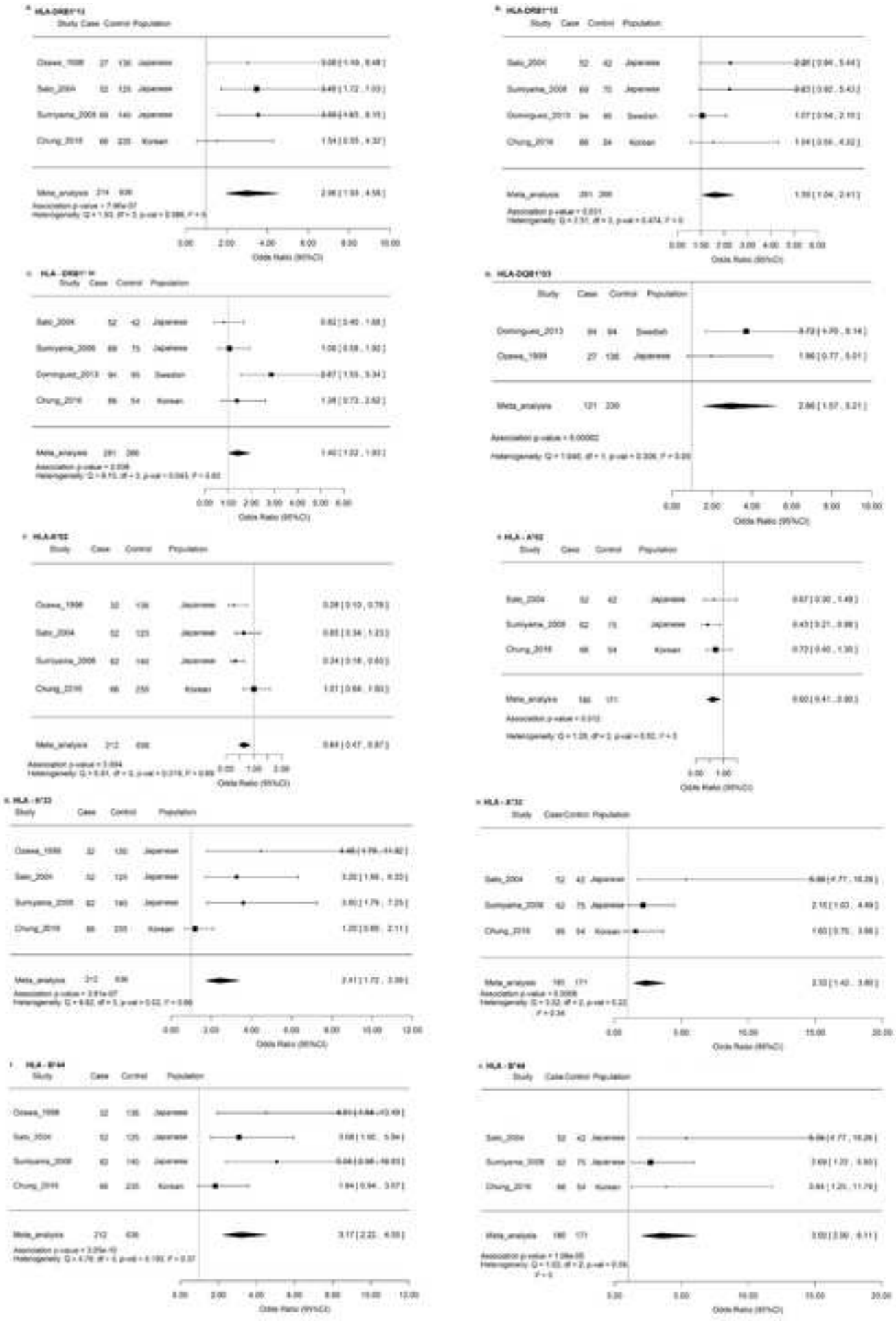


Figure 6

Click here to download Figure Figure6_forestplots_HLA.jpg



Table

A systematic review and meta-analysis of genetic risk factors for neuropathic pain

Table 1. Characteristics of included studies in the systematic review.

Year	Study	Study type	Ethnicity	Sample size (cases/controls)	Mean Age (cases/controls)	Sex (M:F)	NP case definition	NP condition	Control definition
2005	*Armero et al.* (1)	CGAS	Spanish	283 (144/139)	NR	NR	Diagnosis of NP	NP of different aetiology	Healthy subjects without a history of pain
2011	*Binder et al.*(2)	CGAS	German	624 (371/253)	56.4/27.6	157:214/80:173	Expert physician examination; QST	NP of different aetiology	Healthy volunteers
2010	*Cheng et al.*(3)	CGAS	Taiwan	65 (15/50)	67.5/65	11:4/26:24	Diabetics patients had foot ulceration at least 4 weeks and Grades 3-5 pain occurrence; diagnosed by foot tests and VAS for pain intensity ≥ 4	DFU patients with pain	Painless DFU patients (VAS for pain intensity ≤ 3)
2016	*Chung et al.* (4)	CGAS	Korean	355 (66/54,235)	64.7/53.7	34:32/20:34	Persistent pain > 3 months after HZ onset, received treatment.	PHN	Herpes Zoster without pain, Healthy subjects
2014	*Cui et al.* (5)	CGAS	Han Chinese	524 (244/280)	55/54.9	100:144/112:168	Screening: Idiopathic TN. Facial pain: IASP criteria. Clinical, Neurological examination	TN	Healthy volunteers
2011	*Dabby et al.*(6)	Genetic studies	Jewish, Israel	59 (9/50)	NR	NR	Clinical, neurological, MRI examination, QST, VAS pain intensity scale	Chronic severe NP	Healthy controls

2013	*Dominguez et al.* (7)	CGAS	Swedish	189 (94/95)	21-86 years	179:10	Inguinal Pain Questionnaire collection after 6 months of surgery, clinical examination by physician; pain	PPSP after inguinal surgery	Pain-free after inguinal surgery
2013	*Fernandez-de-las-Penas et al.* (8)	CGAS	Spanish	108 (58/50)	44/45	29:29/20:30	Screening: MS with EDSS score and clinical questionnaire - neurogenic pain location intensity	NP due to MS	MS patients without pain
2013	Fernandez-de-las-Penas C et al. (9)	CGAS	Spanish	218 (109/109)	47/46	0:109/0:109	Screening: CTS by clinical and electrophysiological examination, pain score using BCTQ	NP due to CTS	Healthy women without any upper extremity symptom
2014	*Harrer et al.* (10)	Genetic mutation analysis	Caucasian	2 (2/-)	46/-	0:2/-	Clinical evaluation and electrophysiological testing	Nerve pain	-
2012	*Hegarty et al.* (11)	CGAS	European	52 (20/32)	40/39	9:11/19:14	Presence of pain reported 3 months after surgery. Higher pain score compared to pre-operative pain score (VAS score), Neurological examination - MRI & positive straight leg testing, Neurophysiological assessment - QST	PPSP after lumbar discectomy	Individuals without pain after lumbar discectomy
2014	*Huang et al.* (12)	Genetic mutation analysis	Netherlands and UK	1039 (345/694)	49/-	NR	Screening: possible painful peripheral neuropathy	Painful peripheral neuropathy	Healthy controls

2013	*Jacobsen M et al.* (13)	CGAS	Norway (European white)	510 (257/253)	41/41	137:120/131:122	Lumbar disc herniation ; Follow-up examination sensory, motor, lower limb and MRI	Low back pain, Sciatica pain	Pain-free controls without a history of back disease
2012	*Jacobsen et al.* (14)	CGAS	European Caucasian	507 (258/249)	41/41	138:120/129:120	Neurological examination – MRI & positive straight leg testing	Sciatica pain after disc herniation surgery	Healthy subjects without of history of pain and back disease
2014	*Kallianpur et al.* (15)	CGAS	Non-Hispanic blacks or non-Hispanic whites	558 (168/390)	46/43	125:43/316:74	Screening: DPN due to HIV-SN, clinical examination by experts and self-reported questionnaire reported bilateral presence of pain symptoms	DNP due to HIV-SN	Controls without any sensory pain signs or symptoms of peripheral nerve disease
2016	Kalliomaki *et al.* (16)	CGAS	Swedish	140 (47/93)	55.4/58	41:6/87:6	Inguinal pain questionnaire, clinical examination – sensory test	PPSP (probable NP)	Patients without pain after the surgery
2015	*Li et al.*(17)	CGAS	European ancestry (US and Canada)	1916 (887/1029)	59.8/>54	NR	Screening: DPN symptoms using neurological examination PDPN – pain scored by clinical assessment	PDPN	Subjects not having NP
2014	*Meng et al.* (18)	GWAS	Scottish	3063 (572/2491)	66.82/66.86	297:275/1503:988	Screening: Diabetic neuropathy. Monofilament test, first-line NP drugs	PDPN	Diabetic patients without an record of first-line drugs or any opioid drugs for NP
2015	*Meng et al.* (19)	GWAS	Scottish	4221 (961/3260)	72.6/75.5	470:491/2021:1239	Multiple prescriptions : First-line drugs for painful diabetic	PDPN	Diabetic patients without an record of first-line drugs

							peripheral neuropathy (PDPN)		
2010	*Nissenbaum et al.* (20)	CGAS	Israeli Jewish	549 (215/334)	52.9	0:549	Pain after unilateral mastectomy; pain reported by patients during interview	PPSP after mastectomy	Women undergone mastectomy without pain
2005	*Noponen-Hietala et al.* (21)	CGAS	Finnish	334 (155/179)	44/39	94:61/56:123	Unilateral shooting sciatic pain - Clinical presentation and MRI examination, VAS and Oswestry disability scale	Sciatica pain	Healthy subjects
1999	*Ozawa et al.* (22)	CGAS	Japanese	168 (32/136) 163 (27/136)	74.8/-	14:18/-	Screening: PHN (duration of disease 3 to 244 months)	PHN	Healthy subjects
2012	*Ramirez et al.* (23)	Genetic mutation analysis	Caucasian population	2 (2/-)	Age onset 1st to 4th decade	female	QST examination , Validated scale assessment for assessing impairment in CMT – CMTNS, QST, Skin biopsy	Definite NP due to CMT	Healthy controls
2002	*Sato et al.* (24)	CGAS	Japanese	165 (40/125)	68.3/40	17:23/75:50	PHN defined as revisit >90 days after onset, received treatment. VAS score >50	PHN	Healthy subjects without medication and a history of herpes zoster
2004	*Sato-Takeda et al.* (25)	CGAS	Japanese	239 (52/(42,125))	70.1/58.3,44.5	21:31/17:25,75:50	Persistent pain > 3 months after HZ onset, received treatment. VAS score >30	PHN	Herpes Zoster without pain, Healthy subjects

2014	*Stephens et al.* (26)	CGAS	Multiple ethnicity (USA)	172 (46/126)	52.4/58.6	0:46/0:126	Screening: Adult woman who had undergone breast cancer surgery and pain ratings using questionnaire	NP after breast removal surgery; pain score above 6	No pain after breast removal surgery; Pain score 0
2008	*Sumiyama et al.* (27)	CGAS	Japanese	348 (70/(80,52,140))	NR	NR	Persistent pain > 3 months after HZ onset	PHN	PHN^-, $Herpes\ Zoster^-$, Healthy subjects
2012	*Wadley et al.* (28)	CGAS	South Africans	159 (144/15)	41/41	35:124	Screening: HIV-SN Bilateral presence of at least 1 NP pain symptom and clinical sign (vibration sense test); pain intensity score	HIV-SN patients with pain	HIV-SN patients without pain
2017	*Warner et al.* (29)	GWAS	**Discovery** United Kingdom **Replication** United Kingdom Netherlands	**Discovery** 613 (109/504) **Replication** 212 (30/182) 908 (192/716)	NR	NR	Screening: NP in individuals with post-total hip or knee replacement identified by pain DETECT questionnaire. Score > 19 and anti-neuropathic medication	PPSP after hip/knee replacement surgery	Patients without pain after the surgery

CTS, carpal tunnel syndrome; CMT, Charcot Marie tooth syndrome; DFU, diabetic foot ulcer; DPN, distal painful peripheral neuropathy; HIV-SN, human immunodeficiency virus – sensory neuropathy; MS, multiple sclerosis; NP, neuropathic pain; PHN, postherpetic neuralgia; HZ, Herpes Zoster; PDPN, painful diabetic peripheral neuropathy; PPSP, persistent post-surgical pain; TN, trigeminal neuralgia. CGAS, candidate genetic association study; GWAS, genome-wide association study; QST, quantitative sensory testing; IASP, international association for the study of pain; EDSS, Expanded Disability Status Scale; MRI, magnetic resonance imaging; NR, not reported; sample size – number of samples included for genetic association studies.

Table 2. Summary of reported statistical methods, and outcomes from all included studies and estimated quality score for each study.

Year	Study	Genotype method	Genetic markers	HWE	Effect allele	Analysis	Adjusted to covariates	OR (95% CI) / P-value	Outcome	STREGA score (Maximum score =30)
2005	*Armero et al.* (1)	PCR	Chr22q11 Val158Met	NR	A	Chi-Square test	-	**COMT** Not given; Calculated 1.03(0.74–1.44)/0.9	Not associated with NP	19
2011	*Binder et al.*(2)	Pyrosequencing	**TRPA1** rs13268757 rs920829 rs959976 **TRPV1** rs8065080 rs222747 **TRPM8** rs13004520 rs2890163 rs11562975 rs17868387 rs7593557 rs17862932	Y	C G A A C G A G A G C	Chi-Square test and Yates corrected	-	**TRP genes** P = not significant	Not associated with NP	21
2010	*Cheng et al.* (3)	PCR	**OPRM1** A118G rs1799971	Y	G	Fisher's exact test/ Chi-Square test	-	**OPRM1** 0.24(0.07-0.8)/0.038	Associated with DFU pain	23
2016	*Chung et al.* (4)	PCR	SNPs in HLA-A, -B, -C, HLA-DRB1	NR	-	Fisher's exact test/ Chi-Square test	-	**HLA-B*44 PHN vs HZ** 3.84(1.25-11.79)/0.012 **PHN vs controls** 1.83(0.99-3.40)/0.049 **HLA-B*15 PHN vs controls**	Associated with PHN	25

								3.68(1.17-11.61)/0.029 **HLA-C*01** **PHN vs controls** 0.54(0.29-0.98)/0.004 **HLA-C*12** **PHN vs controls** 0.11/0.048 **HLA-DRB1*01** **PHN vs controls** 0.19(0.05-0.81)/0.01 **HLA-DRB1*10** **PHN vs controls** 4.86(1.07-22)/0.04		
2014	*Cui et al.* (5)	PCR	5-HTTLPR rs25531	Y Y	Short A	Multi-variate logistic regression	Age, sex, smoking status	**SLC6A4** **5-HTTLPR** 1.891(1.478-2.418)/0.045 **rs25531** 0.99(0.774-1.258)/0.913	5-HTTLPR associated with TN susceptibility and pain severity Not associated with TN	26
2011	*Dabby et al.* (6)	PCR, fluorescently labelled dideoxynucleosi de terminators	W1550R mutation	-	-	Mutation analysis	-	**SCN9A**	Gain-of-function mutation	NA
2013	*Dominguez et al.* (7)	PCR,Human660-Quad Illumina chip HLA*IMP	DRB1*04, DQB1*03:02	NR	-	Chi-Square test, Bonferroni corrections	-	**DRB1*04** 2.28(1.32-3.96) / 0.05 **DQB1*03:02** 3.16(1.61-6.22) / 0.01	HLA variants associated with risk of developing NP	24
2013	*Fernandez-de-las-Penas et al.* (8)	TaqMan drug metabolism	rs4680 Val158Met	Y	A	Chi-Square test	-	**MS with pain vs. without pain** **COMT**	Associated with NP in MS	23

		genotype assay, real time PCR						P=0.046		
2013	Fernandez-de-las-Penas *et al.* (9)	TaqMan	rs4680 Val158Met	Y	A	Chi-Square test	-	**Carpal Tunnel Syndrome COMT** P=0.780 Calculated 0.9(0.62-1.32)	Not associated with pain susceptibility (CTS) Associated with pain severity	23
2014	*Harrer et al.* (10)	PCR/Sequencing	R1150W variant	-	-	Sequence comparison with reference genome	-	**SCN9A** -	Missense mutations of $Na_v1.9$	NA
2012	*Hegarty et al.* (11)	TaqMan	rs3783641 **rs8007267**, rs10483639, rs1799971, rs4680, rs3892097	NR	T C G A A C	Pearson's' Chi-Square test	-	**GCH1 – CC** P=0.02, **OPRM1, COMT, CYP2D6** P=not significant	A SNP in GCH1 associated with NP Not associated with NP	21
2014	*Huang et al.* (12)	PCR	SCN11A variants	-	-	Sequence comparison with healthy controls	-	**SCN11A** -	R1150W substitution of the $Na_v1.7$. Gain-of-function mutation	NA
2013	*Jacobsen et al.* (13)	TaqMan	rs1799750	Y	G	Chi-Square test	-	**MMP1** P=0.819	Not associated with NP susceptibility but with pain severity	23
2012	*Jacobsen et al.* (14)	TaqMan	rs4680 Val158Met	Y	A	Chi-Square test	-	**COMT** P=0.143	Not associated with NP Associated with pain progression	23

2014	*Kallianpur et al.* (15)	Affymetrix 6.0	rs2718796 rs8177306 rs13072552 rs13075921 rs3816893 rs480760 rs270388 rs267202 rs267206 rs7033149 rs4495514 rs2026739 rs3793451 rs224446 rs16966334 rs1901531	NR	G G T C T T T A C G T G T T G C	Multi-variate logistic regression, Pearson's Chi-Square test Multiple testing	Age, total D-drug exposure, CD4+ T-cell nadir, plasma HIV RNA concentration, all 4 PCAs	**TF** 3.1 (1.4–7.3)/ 0.007 0.4 (0.2–0.9)/ 0.023 **CP** 1.6 (1.1–2.4)/ 0.007 1.6 (1.0–2.4)/ 0.048 1.9 (1.2–3.0)/ 0.004 **TFRC** 0.6 (0.4–0.9)/ 0.042 **BMP6** 1.3 (1.0–1.8)/ 0.057 0.8 (0.6–1.0)/ 0.050 1.4 (1.0–2.0)/ 0.029 **ACO1** 1.6 (1.1–2.4)/ 0.013 0.4 (0.2–0.9)/ 0.040 1.5 (1.1–2.0)/ 0.009 **FXN** 0.4 (0.2–0.9)/ 0.046 **SLC11A2** 0.7 (0.4–1.0)/ 0.047 **B2M** 2.4 (1.3–4.2)/ 0.003 1.6 (1.1–2.5)/ 0.028	8 iron-related genes significantly associated with DPN. Associated with DPN severity	25
2016	*Kalliomaki et al.* (16)	TaqMan	rs1800629 rs5030977 rs6691840 rs6265	NR	G G T G	Chi-Square test	-	**TNF-α** RR(95% CI) 1.93(1.03-3.61)/0.036 **CACNAD2** rs5030977 1.14 (0.66–2.00)/0.603 **GRIK3** 1.16 (0.70–1.92)/0.247 **BDNF** 0.96 (0.58–1.61)/0.340	TNF-α, associated with NP Not associated with NP Not associated with NP Not associated with NP	25

			rs1799971 rs8007267 rs3783641 rs10483639		A A T G			**OPRM1** 0.98 (0.57–1.68)/0.935 **GCH1 haplotype** Not significant	Not associated with NP Not associated with NP	
2015	*Li et al.* (17)	PCR – ligand detection reaction	rs74449889 rs3750904 rs4369876 rs12478318	Y	G C A G	Fisher's exact test/ Chi-Square test	-	**SCN9A** 2.6/0.028 2.2/8.96e-03 2.1/0.047 2.1/0.047	Associated with PDPN susceptibility and pain severity	25
2014	*Meng et al.* (18)	Affymetrix 6.0 Illumina 1000G Imputation	rs17428041	Y	C	Fisher's exact test with multiple testing	Gender, BMI	**GFRA2** 0.67(0.57-0.78)/1.77x10^{-7}	Borderline significance with PDPN	25
2015	*Meng et al.* (19)	Affymetrix 6.0 Illumina 1000G Imputation	rs71647933 rs6986153	Y Y	G G	Fisher's exact test with multiple testing; Gender-specific test	Gender, BMI	**ZSCAN20-TLR12P** 1.65(1.36-2.02)/4.88x10^{-7} (All) 2.31(1.68-3.17)/2.7488x10^{-7} (Female) **HMGB1P46** 1.67(1.34-2.08)/8.02x10^{-7} (Male)	Borderline significance with PDPN	26
2010	*Nissenbaum et al.* (20)	PCR	rs4820242 rs2284015 rs2284017 rs2284018 rs1883988	NR	A C C T A	Logistic regression Permutation analysis Haplotype analysis	Ethnicity, Chemotherapy, Surgery type, Years since operation	**CACNG2** P=0.02, P=0.02, P=0.04, P=0.05, P=0.03, **Haplotype blocks (rs4820242,rs2284015, rs2284017)** 1.65(NA)/0.001	Associated with NP	20

2005	*Noponen-Hietala et al.* (21)	PCR	IL-6 rs13306435 (T15A) rs1800797 (G-597A) rs1800795 (G-174C) rs1800796 (G-572C) **TNFA** rs1800629 (G-308-A)	NR	T G G G	Chi-Square test, Haplotype analysis	-	**IL6-T15A** 4.4(1.2-15.7)/0.011 **Haplotype analysis:IL6 GGGA/GGGA or GGGA/other genotypes** 5.4(1.5-19.2)/0.0033 **TNFA** P=NS	Associated with sciatica Not associated with sciatica	19
1999	*Ozawa et al.*(22)	PCR-RFLP Serological testing	HLA class I HLA class II	NR	-	Chi-Square test With Yates' correction	-	**HLA-A*33** P=0.00972 **HLA-B*44** P=0.003499 **Haplotype HLA-A*33-B*44** P=0.000026 **HLA-A*33-B*44 -DRB1*1302** P=0.002089	Associated with PHN	17
2012	*Ramirez et al.* (23)	cDNA sequence	Trp101X mutation	-	-	Genetic analysis	-	**MPZ**	Trp101X mutation in exon 3 coding portion of MPZ gene	NA
2002	*Sato et al.* (24)	PCR-microtitre plate hybridization method	SNPs in HLA-A, -B allele, HLA-DRB1, TNFA, NKp30	NR	-	Fisher's exact test Multiple testing	-	**HLA-A*3303** 3.27(NA)/0.008 **HLA-B*4403** 3.10(NA)/0.018 **HLA-DRB1*1302** 3.36(NA)/0.019 **Haplotype HLA-A*33-B*44 -DRB1*1302** P=0.0039	HLA alleles, haplotypes associated with PHN	19

2004	*Sato-Takeda et al.* (25)	PCR-Sequence specific primers	SNPs in HLA-A, -B allele, HLA-DRB1	NR	-	Chi-Square test Fisher's exact test Multiple testing	-	a)**PHN vs. ctrl** **A*3303** 3.24/0.0036 **B*4403** 3.07/0.011 **DRB1*1302** 3.45/0.022 **Haplotype A*3303- B*4403-DRB1*1302** 3.52/0.001 b) **PHN vs. HZ** **A*3303** 4.88/0.014 **B*4403** 4.88/0.026 **DRB1*1302** 2.18/0.063 **Haplotype A*3303- B*4403-DRB1*1302** 3.34/0.019	Positive association between PHN and healthy, non-PHN HZ A*3303-B*4403-DRB1*1302 Haplotype – risk factor for PHN	19
2014	*Stephens et al.* (26)	Illumina Golden gate	rs11674595 IL10 haplotypes rs3024505-rs3024496-rs1878672-rs1518111-rs1518110-rs3024491	Y	T	GLM logistic regression, Chi-Square test, haplotype analysis	PCAs, occurrence of breast pain before surgery, severity of average post-operative pain	**IL1 receptor 2** P<0.0001 **IL10 haplotype A8** P<0.0001	Associated with PPSP	25
2008	*Sumiyama et al.* (27)	PCR-Sequence specific oligonucleotide probes	HLA-A, -B allele, HLA-DRB1	NR	-	Chi-Square test With Yates' correction, Multiple testing	-	**PHN+ vs ctrl** **HLA-A*3303** 4.27/0.0007 **HLA-A*02** 0.26/0.001 **HLA-B*4403**	Associated with PHN	20

								6.14/0.00005 **DRB1*1302** 4.05/0.007 **PHN+ vs PHN-** **HLA-A*3303** 2.44/0.03 **HLA-A*02** 0.36/0.009 **HLA-B*4403** 3.14/0.006 **DRB1*1302** 2.69/0.03		
2012	*Wadley et al.* (28)	Illumina BeadXpress	rs10483639, rs3783641, rs8007267	Y	-	Chi-Square test with multiple correction	Age, gender, CD4+ T-cell count	**GCH1** P=NS **GCH1** **3-SNP haplotypes** P=0.05; adjusted P-value = 0.08	Individual SNPs – not associated with NP. Positive results/not significant after correction	23
2017	*Warner et al.* (29)	Illumina 610 k array	rs887797	Y	A	Chi-square test with multiple correction **Meta-analysis** Han Eskin random effects model	Age, gender, BMI	**Discovery** **PRKCA** 2.00 (1.48-2.70) / P=4.29x10^{-6} **Combined** 2.41 (1.74-3.34) / 1.65×10^{-5} (recessive model)	Suggestive signal; associated with NP	27

CTS, carpal tunnel syndrome; CMT, Charcot Marie tooth syndrome; DFU, diabetic foot ulcer; DPN, distal painful peripheral neuropathy; HIV-SN, human immunodeficiency virus – sensory neuropathy; HZ, Herpes Zoster; MS, multiple sclerosis; NP, neuropathic pain; PDPN, painful diabetic peripheral neuropathy; PHN, postherpetic neuralgia; PPSP, persistent post-surgical pain; TN, trigeminal neuralgia. CI, confidence interval; HWE, Hardy-Weinberg equilibrium; OR, odds-ratio, PCR, polymerase chain reaction; PCA, principal component analysis; SNP, single nucleotide polymorphisms; STREGA, strengthening of reporting the genetic association studies. NR, not reported; NS, not significant. Grey rows, studies included in the meta-analysis; Non shaded rows, studies not included in the meta-analysis.

Table 3. Summary of candidate genes and functional effects of genetic variants reported in this review.

Gene Symbol	Gene Name	Pathway	Function	SNP (Locus)	Transcriptional Regulation (Regulome DB)	Epigenetic regulation (ENCODE)	SNP function (dbSNP, Haploreg)	NP condition	Studies (n)
OPRM1	Mu-type opioid receptor	Neurotransmission, Neuroactive ligand-receptor interaction, Opioid proenkephalin	G-protein coupled receptor activity voltage-gated calcium channel activity	rs1799971 (chr6q25.2)	Minimal protein binding NRSF, CTBP2	Lies in DNase sensitivity, promoter histone and enhancer; hsa-miR-152	Missense	PDPN, PPSP	3
COMT	Catechol O-methyltransferase	Neurotransmission	Metabolize catecholamine neurotransmitter	G1947A, rs4680 (chr22q11)	Transcription factor binding POLR2A / NR4A1	Lies in DNase sensitivity, promoter histone and enhancer	Missense	Multiple aetiologies MS, CTS, Sciatica	5
SCN9A	Sodium channel, voltage-gated, type IX, alpha subunit	Neurotransmission, Neuropathic-pain signalling in dorsal horn neurons	Voltage-gated ion channel activity	rs74449889 (chr2q24.3) rs3750904 rs4369876 rs12478318	Minimal binding evidence	hsa-miR-152	Intronic Missense Missense Missense	PDPN	1
SLC6A4	Solute carrier family 6, member 4	Transporters, 5HT2 type receptor mediated signalling pathway, Neurotransmission	Serotonin: sodium symporter activity neurotransmitter transport	5-HTTLPR short rs25531 (chr17q11.2)	Minimal binding evidence	Lies in promoter and enhancer histone marks	Missense 1.3kb 5' of SLC6A4	TN	1
CACNG2	Calcium channel, voltage-dependent gamma subunit 2 Transmembrane AMPAR Regulatory Protein Gamma-2	Neurotransmission, Pain signalling	Voltage-gated ion channel activity	rs4820242 (chr22q12.3) rs2284015 rs2284017	Minimal binding evidence SETDB1 Minimal binding evidence	Lies in DNase sensitivity and enhancer histone marks Lies in promoter	Intronic	PPSP	1

						histone marks brain tissues			
HLA-A	Major histocompatibility complex, class I, A	Immune response, Antigen processing and presentation	Involved in the presentation of foreign antigens to the immune system	HLA-A*3303 HLA-A*02 (chr6p22.1)	NA	NA	-	PHN	5
HLA-B	Major histocompatibility complex, class I, B-7 alpha chain	Immune response, Antigen presentation	Involved in the presentation of foreign antigens to the immune system	HLA-B*4403 allele (chr6p21.33)	NA	NA	-	PHN	5
HLA-DQB1	Major histocompatibility complex, class II, DQ beta 1	Immune response, Antigen processing and presentation	Involved in the presentation of foreign antigens to the immune system	HLA-DQB1*03:02 allele (chr6p21.32)	NA	NA	-	PPSP	2
HLA-DRB1	Major histocompatibility complex, class II, DR beta 1	Immune response, Peptide antigen binding	Binds peptides derived from antigens	HLA-DRB1*04 HLA-DRB1*13 (chr6p21.32)	NA	NA	-	PHN, PPSP	6
IL6	Interleukin 6	Immune response, Interleukin signalling	Cytokine activity	rs13306435 T15A (exon 5) (chr7p15.3)	Transcription factor Likely affect binding	Lies in DNase sensitivity, foot printing, promoter and enhancer histone marks	Missense	Sciatica	1
IL1R2	Interleukin-1 receptor, Type II	Immune response	Protein binding Decoy receptor to other interleukins	rs11674595 (chr2q11.2)	Minimal binding evidence	Lies in promoter and enhancer histone marks	Intronic	PPSP	1
IL10	Interleukin 10	Immune response, Interleukin signalling	Negative regulation of myeloid dendritic cell activation	rs1518110 (chr1q32.1) rs1518111 rs1878672 rs3024491 rs3024496	Less likely to affect binding	Lies in DNase sensitivity, promoter and enhancer histone marks	Intronic Intronic Intronic Intronic 3'UTR	PPSP	1

				rs3024498 rs3024505	NFKB Strongly likely to affect binding		3'UTR Intronic		
TNF-α	Tumour necrosis factor alpha	Immune response	Cytokine activity	rs1800629 (chr6p21.33)	Strongly likely to affect binding and influences gene expression	Lies in DNase sensitivity, promoter and enhancer histone marks	312bp 5' TNF	PPSP	1
B2M	Beta-2-microglobulin	Immune response, Iron metabolism	Antigen processing and presentation of peptide antigen via MHC class I	rs16966334 (chr15q21.1) rs1901531 (chr15q21.1)	Strongly likely to affect binding Minimal binding evidence	Lies in DNase sensitivity, promoter and enhancer histone marks in fetal brain	Intronic Intronic	DPN	1
BMP6	Bone morphogenetic protein 6	Immune response	Positive regulation of neuron differentiation Cytokine activity	rs270388 (chr6p24.3) rs267202 rs267206	Minimal binding evidence No evidence No evidence	Lies in enhancer histone marks NA NA	Intronic Intronic Intronic	DPN	1
TF	Transferrin	Iron metabolism	Protein binding	rs2718796 (chr3q22.1) rs8177306	Less likely to affect binding Minimal binding evidence	hsa-miR-152 Lies in DNase sensitivity and histone marks	Intronic Intronic	DPN	1
CP	Ceruloplasmin (ferroxidase)	Iron metabolism	Ferroxidase activity /iron binding	rs13072552 (chr3q24) rs13075921 rs3816893 (chr3q25.1)	Minimal binding evidence No evidence	Lies in DNase sensitivity and enhancer histone marks Lies in enhancer histone marks	Non-synonymous Intronic Intronic	DPN	1

TFRC	Transferrin receptor	Iron metabolism	Chaperone binding	rs480760 (chr3q29)	Less likely to affect binding	Lies in DNase sensitivity and enhancer histone marks	Intronic	DPN	1
ACO1	Aconitase 1, soluble	Iron metabolism	Iron-responsive element binding	rs7033149 (chr9p21.1)	Likely to affect binding and linked to gene expression	Lies in DNase sensitivity and enhancer histone marks	Intronic	DPN	1
				rs4495514	Minimal binding evidence	Lies in DNase (thymus) sensitivity and enhancer histone marks	Intronic		
				rs2026739	No evidence	-	Intronic		
FXN	Frataxin	Iron metabolism	Ferroxidase activity /iron binding	rs3793451 (chr9q21.11)	Minimal binding evidence	Lies in DNase sensitivity and enhancer histone marks; hsa-miR-152	Intronic	DPN	1
GCH1	GTP cyclohydrolase 1	Metabolism Tetrahydrofolate biosynthesis, Neurotransmission	GTP-dependent protein binding	rs752688 (chr14q22.2)	Minimal binding evidence	Lies in DNase sensitivity and enhancer histone marks	Intronic	PPSP, pain due to HIV-SN	2
				rs3783641	Likely to affect binding	Lies in DNase sensitivity, promoter and enhancer histone marks	Intronic		
				rs8007201	Less likely to affect binding (EBF1, PU1, MEF2A)		Intronic		
SLC11A2	Solute carrier family 11 member 2	Transporters, Iron metabolism	Transmembrane transporter activity	rs224446 (chr12q13.12)	Minimal binding evidence	Lies in enhancer histone marks	3’ UTR	DPN	1

GFRA2	GDNF family receptor alpha 2	Receptor signalling, Immune response	Gial cell-derived neurotrophic factor receptor activity	rs17428041 (chr8p21.3)	Minimal binding evidence	Lies in enhancer histone marks	42kb 5' of GFRA2	PDPN	1
HMGB1P46	High mobility group box 1	Immune response	Cytokine activity	rs6986153 (chr8q23.1)	-	-	190 kb 3' of ANGPT1	PDPN	1
ZSCAN20	Zinc finger and SCAN domain containing 20	Ion binding	Transcription factor activity	rs71647933 (chr1p35.1)	No evidence	-	Intronic	PDPN	1
PRKCA	Protein kinase C, alpha	Receptor signalling, Apoptosis signalling	Signal transduction Protein binding	rs887797 (chr17q24.2)	Minimal protein binding EP300	Lies in DNase sensitivity in fetal lung, promoter histone mark in fetal brain and enhancer	Intronic	PPSP	1
TRPA1	Transient receptor potential cation channel, subfamily A, member 1	Transporters, Neurotransmission	Thermoception	rs920829 (chr8q21.11)	No evidence	-	Missense	Multiple aetiology	1
TRPV1	Transient receptor potential vanilloid 1	Ion channel activity, Neurotransmission	Thermoception	rs222747 (chr17p13.2) rs8065080	Minimal binding evidence	Lies in DNase sensitivity	Missense	Multiple aetiology	1
TRPM8	Transient receptor potential subfamily M member 8	Ion channel activity, Neurotransmission	Ion channel	rs13004520 (chr2q37.1) rs11562975 (chr2q37.1)	No evidence No evidence	Lies in enhancer histone marks Lies in enhancer histone marks	Missense Synonymous	Multiple aetiology	1

CYP2D6	Cytochrome P450 Family 2 Subfamily D Member 6	Drug metabolism	Oxidoreductase activity, Drug binding	rs3892097 (chr22q13.2)	Minimal binding evidence	Lies in promoter histone marks liver tissue and enhancer histone marks	Splice donor	PPSP	1
MMP1	Matrix metallopeptidase 1	Ion binding	Protein degradation	rs1799750 (chr11q22.3)	Minimal binding evidence Protein bound CFOS, GATA2	Lies in DNase sensitivity, enhancer histone marks; hsa-miR-22	1.6 kb 5' of MMP1	Sciatica	1
CACNA2D2	Calcium Voltage-Gated Channel Auxiliary Subunit Alpha2delta 2	Transporters	Voltage-gated ion channel activity	rs5030977 (chr3p21.31)	Affect transcription binding	Lies in enhancer histone marks	Intronic	PPSP	1
GRIK3	Glutamate ionotropic receptor kainite type subunit 3	Glutamate receptor, Neuroactive ligand-receptor interaction	Ion channel activity	rs6691840 (chr1p34.3)	Minimal binding evidence	Lies in enhancer histone marks	Missense	PPSP	1
BDNF	Brain-derived neutrophic factor	Receptor signalling	Nervous system development	rs6265 (chr11p14.1)	Minimal binding evidence	Overlaps with promoter and enhancer histone marks	Missense	PPSP	1

CTS, carpal tunnel syndrome; CMT, Charcot Marie tooth syndrome; DFU, diabetic foot ulcer; DPN, distal painful peripheral neuropathy; HIV-SN, human immunodeficiency virus – sensory neuropathy; HZ, Herpes Zoster; MS, multiple sclerosis; NP, neuropathic pain; PDPN, painful diabetic peripheral neuropathy; PHN, postherpetic neuralgia; PPSP, persistent post-surgical pain; TN, trigeminal neuralgia. UTR, untranslated region; SNP, single nucleotide polymorphisms; Chr, chromosome; MHC, major histocompatibility complex. Genes that are significantly associated with NP are in bolded text.

References

1. Armero P, Muriel C, Santos J, Sanchez-Montero FJ, Rodriguez RE, Gonzalez-Sarmiento R. COMT (Val158Met) polymorphism is not associated to neuropathic pain in a Spanish population. Eur J Pain. 2005;9(3):229–32.

2. Binder A, May D, Baron R, Maier C, Tolle TR, Treede RD, et al. Transient receptor potential channel polymorphisms are associated with the somatosensory function in neuropathic pain patients. PLoS One. 2011;6(3).

3. Cheng KI, Lin SR, Chang LL, Wang JY, Lai CS. Association of the functional A118G polymorphism of OPRM1 in diabetic patients with foot ulcer pain. J Diabetes Complicat. 2010;24(2):102–8.

4. Chung HY, Song EY, Yoon JA, Suh DH, Lee SC, Kim YC, et al. Association of human leukocyte antigen with postherpetic neuralgia in Koreans. Apmis. 2016;124(10):865–71.

5. Cui W, Yu X, Zhang H. The serotonin transporter gene polymorphism is associated with the susceptibility and the pain severity in Idiopathic Trigeminal Neuralgia patients. J Headache Pain. 2014;15(1):42.

6. Dabby R, Sadeh M, Gilad R, Lampl Y, Cohen S, Inbar S, et al. Chronic non-paroxysmal neuropathic pain - Novel phenotype of mutation in the sodium channel SCN9A gene. J Neurol Sci. 2011;301(1–2):90–2.

7. Dominguez CA, Kalliomaki M, Gunnarsson U, Moen A, Sandblom G, Kockum I, et al. The DQB1*03:02 HLA haplotype is associated with increased risk of chronic pain after inguinal hernia surgery and lumbar disc herniation. Pain. 2013;154(3):427–33.

8. Fernández-de-las Peñas C, Ambite-Quesada S, Ortíz-Gutiérrez R, Ortega-Santiago R, Gil-Crujera A, Caminero AB. Catechol-O-methyltransferase val158met polymorphism (rs4680) Is associated with pain in multiple sclerosis. J Pain. 2013;14(12):1719–23.

9. Fernandez-de-las-Penas C, Ambite-Quesada S, Ortega-Santiago R, Martinez-Perez A, Diaz HF, Martinez-Martin J, et al. Catechol-O-methyltransferase val158met polymorphism is associated with pain and disability, but not widespread pressure pain sensitivity, in women with carpal tunnel syndrome. Pain Physician. 2013;16(5):E591–600.

10. Harrer JU, Üçeyler N, Doppler K, Fischer TZ, Dib-Hajj SD, Waxman SG, et al. Neuropathic pain in two-generation twins carrying the sodium channel Nav1.7 functional variant R1150W. Pain. 2014;155(10):2199–203.

11. Hegarty D, Shorten G. Multivariate prognostic modeling of persistent pain following lumbar discectomy. Pain Physician. 2012;15(5):421–34.

12. Huang J, Han C, Estacion M, Vasylyev D, Hoeijmakers JGJ, Gerrits MM, et al. Gain-of-function mutations in sodium channel Na(v)1.9 in painful neuropathy. Brain. 2014;137:1627–42.

13. Jacobsen LM, Schistad EI, Storesund A, Pedersen LM, Espeland A, Rygh LJ, et al. The MMP1 rs1799750 2G allele is associated with

increased low back pain, sciatica, and disability after lumbar disk herniation. Clin J Pain. 2013;29(11):967–71.

14. Jacobsen LM, Schistad EI, Storesund A, Pedersen LM, Rygh LJ, Roe C, et al. The COMT rs4680 Met allele contributes to long-lasting low back pain, sciatica and disability after lumbar disc herniation. Eur J Pain. 2012;16(7):1064–9.

15. Kallianpur AR, Jia P, Ellis RJ, Zhao Z, Bloss C, Wen W, et al. Genetic variation in iron metabolism is associated with neuropathic pain and pain severity in HIV-infected patients on antiretroviral therapy. PLoS One. 2014;9(8).

16. Kalliomäki ML, Sandblom G, Hallberg M, Grönbladh A, Gunnarsson U, Gordh T, et al. Genetic susceptibility to postherniotomy pain. The influence of polymorphisms in the Mu opioid receptor, TNF-α, GRIK3, GCH1, BDNF and CACNA2D2 genes. Scand J Pain. 2016;12:1–6.

17. Li QS, Cheng P, Favis R, Wickenden A, Romano G, Wang H. SCN9A variants may be implicated in neuropathic pain associated with diabetic peripheral neuropathy and pain severity. Clin J Pain. 2015;31(11):976–82.

18. Meng W, Deshmukh H, Donnelly LA, van Zuydam NR, Liu Y, Zhou K, et al. A genome-wide association study suggests an association of Chr8p21.3 (GFRA2) with diabetic neuropathic pain. Eur J Pain. 2015;19(3):392–9.

19. Meng W, Deshmukh H., Donnelly LA, Torrance N, Colhoun HM, Palmer CNA, et al. A Genome-wide Association Study Provides Evidence of Sex-specific Involvement of Chr1p35.1 (ZSCAN20-TLR12P) and Chr8p23.1 (HMGB1P46) With Diabetic Neuropathic Pain. EBioMedicine. 2015;2(10):1386–93.

20. Nissenbaum J, Devor M, Seltzer Z, Gebauer M, Michaelis M, Tal M, et al. Susceptibility to chronic pain following nerve injury is genetically affected by CACNG2 Susceptibility to chronic pain following nerve injury is genetically affected by CACNG2. Genome Res. 2010;20:1180–90.

21. Noponen-Hietala N, Virtanen I, Karttunen R, Schwenke S, Jakkula E, Li H, et al. Genetic variations in IL6 associate with intervertebral disc disease characterized by sciatica. Pain. 2005;114(1–2):186–94.

22. Ozawa A, Sasao Y, Iwashita K, Miyahara M, Sugai J, Iizuka M, et al. HLA-A33 and -B44 and susceptibility to postherpetic neuralgia (PHN). Tissue Antigens. 1999;53(3):263–8.

23. Ramirez JD, Barnes PRJ, Mills KR, Bennett DLH. Intermediate Charcot-Marie-Tooth disease due to a novel Trp101Stop myelin protein zero mutation associated with debilitating neuropathic pain. Pain. 2012;153(8):1763–8.

24. Sato M, Ohashi J, Tsuchiya N, Kashiwase K, Ishikawa Y, Arita H, et al. Association of HLA-A*3303-B*4403-DRB1*1302 haplotype, but not of TNFA promoter and NKp30 polymorphism, with postherpetic neuralgia (PHN) in the Japanese population. Genes Immun. 2002;3(8):477–81.

25. Sato-Takeda M, Ihn H, Ohashi J, Tsuchiya N, Satake M, Arita H, et al. The human histocompatibility leukocyte antigen (HLA) haplotype is

associated with the onset of postherpetic neuralgia after herpes zoster. Pain. 2004;110(1–2):329–36.

26. Stephens K, Cooper B a, West C, Paul SM, Christina R, Merriman JD, et al. Associations between cytokine gene variations and severe persistent breast pain in women following breast cancer surgery. J Pain. 2014;15(2):169–80.

27. Sumiyama D, Kikkawa EF, Kita YF, Shinagawa H, Mabuchi T, Ozawa A, et al. HLA alleles are associated with postherpetic neuralgia but not with herpes zoster. Tokai J Exp Clin Med. Japan; 2008;33(4):150–3.

28. Wadley AL, Lombard Z, Cherry CL, Price P, Kamerman PR. Analysis of a Previously Identified "Pain-Protective" Haplotype and Individual Polymorphisms in the GCH1 Gene in Africans With HIV-Associated Sensory Neuropathy. JAIDS J Acquir Immune Defic Syndr. 2012;60(1):20–3.

29. Warner SC, van Meurs JB, Schiphof D, Bierma-Zeinstra SM, Hofman A, Uitterlinden AG, et al. Genome-wide association scan of neuropathic pain symptoms post total joint replacement highlights a variant in the protein-kinase C gene. Eur J Hum Genet. 2017;44:1–6.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3-4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4 & Table S2
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4 & & Table S1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4-5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5 & Table 1
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Table 2
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	5
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6 & Fig.1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6-7
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	7 & Table S4 & S5
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	7-14
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	7-14
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	8-10
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Table 3
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	14-17
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	16-17
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	18
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	18

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

A systematic review and meta-analysis of genetic risk factors for neuropathic pain

Supplementary tables

Table S1. Search strategy used

Search terms	Combined Keywords using Boolean operators
Neuropathic pain	"neuropathic pain" OR "neurogenic pain" OR "neuropath* pain" OR "painful peripheral neuropathy" OR "neuralgia [MeSH Terms]" OR "nerve pain" OR "pain [MeSH Terms], neuropathic"
	AND
Genetic factors	"single nucleotide polymorphism* [MeSH Terms]" OR "genetic polymorphism [MeSH Terms]" OR "allele" OR "genetic variation [MeSH Terms]" OR "gene variant" OR "mutation [MeSH Terms]" OR "genes [MeSH Terms]" OR "chromosome [MeSH Terms]" OR "genetic predisposition$ [MeSH Terms]" OR "genetic susceptibility"
	OR
Study design	"genetic association studies [MeSH Terms]" OR "genome-wide association study [MeSH Terms]" OR "GWAS" OR "candidate gene study" OR "twin study" OR "genotype [MeSH Terms]" OR "haplotype [MeSH Terms]" OR "heritability*"

Table S2. Inclusion and Exclusion criteria

Inclusion criteria	Exclusion criteria
Studies focus on individuals (adults) with neuropathic pain (NP). Studies on genetic risk factors for neuropathic pain in humans. Genetic studies including genetic association, twin, candidate genes, heritability, and family-based studies. Case-control study design. Studies published in English and peer-reviewed journals.	Studies performed only on animals. Case-only studies, review, and case reports. Patients with cancer pain, and any pain related conditions that are not considered as NP by International Association for the Study of Pain (IASP). Patients with non-neuropathic pain. Studies investigating the genetic determinants of pain severity only.

Table S3. Full-text study exclusion list

Author, Year	Title	Journal	Reason for exclusion
Basol *et al*., 2013 (1)	High Association of IL-4 Gene Intron 3 VNTR Polymorphism with Diabetic Peripheral Neuropathy	Journal of Molecular Neuroscience	Not a NP study
Brasch-Anderson *et al*., 2011 (2)	A candidate gene study of serotonergic pathway genes and pain relief during treatment with escitalopram in patients with neuropathic pain shows significant association to serotonin receptor2C (HTR2C)	Pharmacogenetics, European Journal of Clinical Pharmacology	Not a NP risk factor study
Costigan *et al*., 2010 (3)	Multiple chronic pain states are associated with a common amino acid–changing allele in KCNS1	BRAIN – A Journal of Neurology	Not a NP risk factor study
Dai *et al*., 2010 (4)	Association of catechol-O-methyltransferase genetic variants with outcome in patients undergoing surgical treatment for lumbar degenerative disc disease	The Spine Journal	Not a NP risk factor study
Duan *et al*., 2010 (5)	A single-nucleotide polymorphism in SCN9A may decrease postoperative pain sensitivity in the general population	The American Society of Anaesthesiologists	Not a NP risk factor study
Hendry *et al*., 2013 (6)	KCNS1, but not GCH1, is associated with pain intensity in a black southern African population with HIV-associated sensory neuropathy: a genetic association study	Journal of Acquired Immunodeficiency Syndrome	Not a NP risk factor study
Hendry *et al*., 2016 (7)	TNF Block Gene Variants Associate With Pain Intensity in Black Southern Africans With HIV-associated Sensory Neuropathy	Clinical Journal of Pain	Not a NP risk factor study
Hooten *et al*., 2013 (8)	Associations between serotonin transporter gene polymorphisms and heat pain perception in adults with chronic pain	BMC Medical Genetics	Not a NP study
Ide *et al*., 2014 (9)	Haplotypes of P2RX7 gene polymorphisms are associated with both cold pain sensitivity and analgesic effect of fentanyl	Molecular Pain	Not a NP study
Karppinen *et al*., 2008 (10)	Is the interleukin-6 haplotype a prognostic factor for sciatica?	European Journal of Pain	Not a NP risk factor study
Kim *et al*., 2010 (11)	Polymorphic Variation of the Guanosine Triphosphate Cyclohydrolase 1 Gene Predicts Outcome in Patients Undergoing Surgical Treatment for Lumbar Degenerative Disc Disease	SPINE	Not a NP risk factor study
Kolesnikov *et al*., 2013 (12)	Chronic pain after lower abdominal surgery: do catechol-O-methyl transferase/opioid receptor μ-1 polymorphisms contribute?	Molecular Pain	Not a NP study
Olsen *et al*., 2012 (13)	Pain Intensity the First Year after Lumbar Disc Herniation Is Associated with the A118G Polymorphism in the Opioid Receptor Mu 1 Gene: Evidence of a Sex and Genotype Interaction	The Journal of Neuroscience	Not a NP risk factor study
Reimann *et al*., 2010 (14)	Pain perception is altered by a nucleotide polymorphism in SCN9A	PNAS	Not a NP study

Rooij *et al*., 2009 (15)	HLA-B62 and HLA-DQ8 are associated with Complex Regional Pain Syndrome with fixed dystonia	PAIN	Not a NP study
Rooijen *et al*., 2012 (16)	Genetic HLA Associations in Complex Regional Pain Syndrome With and Without Dystonia	The Journal of Pain	Not a NP study
Rut *et al*., 2009 (17)	Influence of variation in the catechol-O-methyltransferase gene on the clinical outcome after lumbar spine surgery for one-level symptomatic disc disease: a report on 176 cases	Acta Neurochirurgica	Not a NP risk factor study
Schmahl *et al*., 2012 (18)	COMT val158met Polymorphism and Neural Pain Processing	PLoS ONE	Not a NP study
Tegeder *et al*., 2012 (19)	GTP cyclohydrolase and tetrahydrobiopterin regulate pain sensitivity and persistence	Nature Medicine	Not a NP risk factor study
Ursu *et al*., 2014 (20)	Gain and loss of function of P2X7 receptors: mechanisms, pharmacology and relevance to diabetic neuropathic pain	Molecular Pain	Not a NP risk factor study
Yilmaz *et al*., 2014 (21)	Pain in hereditary neuropathy with liability to pressure palsy: an association with fibromyalgia syndrome?	Muscle and Nerve	Not a NP study

References

1. Basol N, Inanir A, Yigit S, Karakus N, Kaya SU. High association of IL-4 gene intron 3 VNTR polymorphism with diabetic peripheral neuropathy. J Mol Neurosci. 2013;51(2):437–41.

2. Brasch-Andersen C, Moller MU, Christiansen L, Thinggaard M, Otto M, Brosen K, et al. A candidate gene study of serotonergic pathway genes and pain relief during treatment with escitalopram in patients with neuropathic pain shows significant association to serotonin receptor2C (HTR2C). Eur J Clin Pharmacol. C. Brasch-Andersen, Department of Clinical Genetics, Odense University Hospital, Odense, Denmark. E-mail: charlotte.b.andersen@ouh.regionsyddanmark.dk: Springer Verlag (Tiergartenstrasse 17, Heidelberg D-69121, Germany); 2011;67(11):1131–7.

3. Costigan M, Belfer I, Griffin RS, Dai F, Barrett LB, Coppola G, et al. Multiple chronic pain states are associated with a common amino acid-changing allele in KCNS1. Brain. England: Oxford University Press (Great Clarendon Street, Oxford OX2 6DP, United Kingdom); 2010;133(9):2519–27.

4. Dai F, Belfer I, Schwartz CE, Banco R, Martha JF, Tighioughart H, et al. Association of catechol-O-methyltransferase genetic variants with outcome in patients undergoing surgical treatment for lumbar degenerative disc disease. Spine J. 2010;10(11):949–57.

5. Duan M.S. G, Guifang X, Xianwei Z, Ruimei Y, Huiming Z, Dongmei Q. A Single-nucleotide Polymorphism in SCN9A May Decrease Postoperative Pain Sensitivity in the General Population. Anesthesiology. 2016;118(2):436–42.

6. Hendry L, Lombard Z, Wadley A, Kamerman P. KCNS1, but not GCH1, is associated with pain intensity in a black southern African population with HIV-associated sensory neuropathy: a genetic association study. J Acquir Immune Defic Syndr. 2013;63(1):27–30.

7. Hendry LM, Wadley AL, Cherry CL, Price P, Lombard Z, Kamerman PR. TNF Block Gene Variants Associate With Pain Intensity in Black Southern Africans With HIV-associated Sensory Neuropathy. Clin J Pain. 2016;32(1):45–50.

8. Hooten WM, Hartman WR, Black III JL, Laures HJ, Walker DL. Associations between serotonin transporter gene polymorphisms and heat pain perception in adults with chronic pain. Bmc Med Genet. 2013;14.

9. Ide S, Nishizawa D, Fukuda K, Kasai S, Hasegawa J, Hayashida M, et al. Haplotypes of P2RX7 gene polymorphisms are associated with both cold pain sensitivity and analgesic effect of fentanyl. Mol Pain. 2014;10.

10. Karppinen J, Daavittila I, Noponen N, Haapea M, Taimela S, Vanharanta H, et al. Is the interleukin-6 haplotype a prognostic factor for sciatica? Eur J Pain. 2008;12(8):1018–25.

11. Kim DH, Dai F, Belfer I, Banco RJ, Martha JF, Tighiouart H, et al. Polymorphic variation of the guanosine triphosphate cyclohydrolase 1 gene

predicts outcome in patients undergoing surgical treatment for lumbar degenerative disc disease. Spine (Phila Pa 1976). 2010;35(21):1909–14.

12. Kolesnikov Y, Gabovits B, Levin A, Veske A, Qin L, Dai F, et al. Chronic pain after lower abdominal surgery: do catechol-O-methyl transferase/opioid receptor mu-1 polymorphisms contribute?. Mol Pain. I. Belfer, Departments of Anesthesiology and Human Genetics, University of Pittsburgh, Pittsburgh, PA, United States. E-mail: belferi@upmc.edu: BioMed Central Ltd. (Floor 6, 236 Gray's Inn Road, London WC1X 8HB, United Kingdom); 2013;9(1):19.

13. Olsen MB, Jacobsen LM, Schistad EI, Pedersen LM, Rygh LJ, Roe C, et al. Pain intensity the first year after lumbar disc herniation is associated with the A118G polymorphism in the opioid receptor mu 1 gene: evidence of a sex and genotype interaction. J Neurosci. 2012;32(29):9831–4.

14. Reimann F, Cox JJ, Belfer I, Diatchenko L, Zaykin D V, McHale DP, et al. Pain perception is altered by a nucleotide polymorphism in SCN9A. Proc Natl Acad Sci U S A. 2010;107(11):5148–53.

15. de Rooij AM, Florencia Gosso M, Haasnoot GW, Marinus J, Verduijn W, Claas FH, et al. HLA-B62 and HLA-DQ8 are associated with Complex Regional Pain Syndrome with fixed dystonia. Pain. 2009;145(1-2):82–5.

16. van Rooijen DE, Roelen DL, Verduijn W, Haasnoot GW, Huygen FJ, Perez RS, et al. Genetic HLA associations in complex regional pain syndrome with and without dystonia. J Pain. 2012;13(8):784–9.

17. Rut M, Machoy-Mokrzyńska A, Ręcławowicz D, Słoniewski P, Kurzawski M, Droadzik M, et al. Influence of variation in the catechol-O-methyltransferase gene on the clinical outcome after lumbar spine surgery for one-level symptomatic disc disease: A report on 176 cases. Acta Neurochir (Wien). 2014;156(2):245–52.

18. Schmahl C, Ludäscher P, Greffrath W, Kraus A, Valerius G, Schulze TG, et al. COMT val158met polymorphism and neural pain processing. PLoS One. 2012;7(1).

19. Tegeder I, Costigan M, Griffin RS, Abele A, Belfer I, Schmidt H, et al. GTP cyclohydrolase and tetrahydrobiopterin regulate pain sensitivity and persistence. Nat Med. 2006;12(11):1269–77.

20. Ursu D, Ebert P, Langron E, Ruble C, Munsie L, Zou W, et al. Gain and loss of function of P2X7 receptors: mechanisms, pharmacology and relevance to diabetic neuropathic pain. Mol Pain. England: BioMed Central Ltd.; 2014;10(1):37.

21. Yilmaz U, Bird TT, Carter GT, Wang LH, Weiss MD. Pain in hereditary neuropathy with liability to pressure palsy: An association with fibromyalgia syndrome? Muscle and Nerve. 2015;51(3):385–90.

Table S4. The quality assessment checklist based on the STREGA guidelines

Item section	Quality score	Quality Criteria
Title & Abstract	1	Study design is clearly stated in title and abstract
Introduction		
Background	2	Background and rationale
Objectives	3	Aim is clearly reported corresponds to the study question
Study selection		
Study design	4	Eligibility criteria, both inclusion and exclusion criteria are specified
Setting	5	Study participants recruitment place, duration and method
Participants	6	Define the study population (participants/non-participants) at each stage, subset from large study
Variables	7	Demographic, clinical, genetic and other relevant information specific to study
Data collection		
Case	8	Phenotype measurement/definition, genotype information, quality control metrics, genotyping method
Control	9	Phenotype measurement/definition, genotype information, quality control metrics, genotyping method
Bias	10	Standardized phenotype assessment method, any potential known bias
Sample size	11	Appropriate case / control sample size appropriate to the study design
Quantitative variables	12	Covariates measurement
Statistical methods	13	Appropriate statistical tests
	14	Genotype information – Hardy Weinberg Equilibrium was considered
	15	Whether genotypes or haplotypes used for analyses
	16	Assessed relatedness and population outliers
Results		
Participants	17	Number of cases passed and failed quality control assessment
	18	Number of controls passed and failed quality control assessment
Descriptive data	19	Case: covariates information presented by genotype information
	20	Control: covariates information presented by genotype information
Outcomes	21	Effect size, confidence intervals, P-value presented

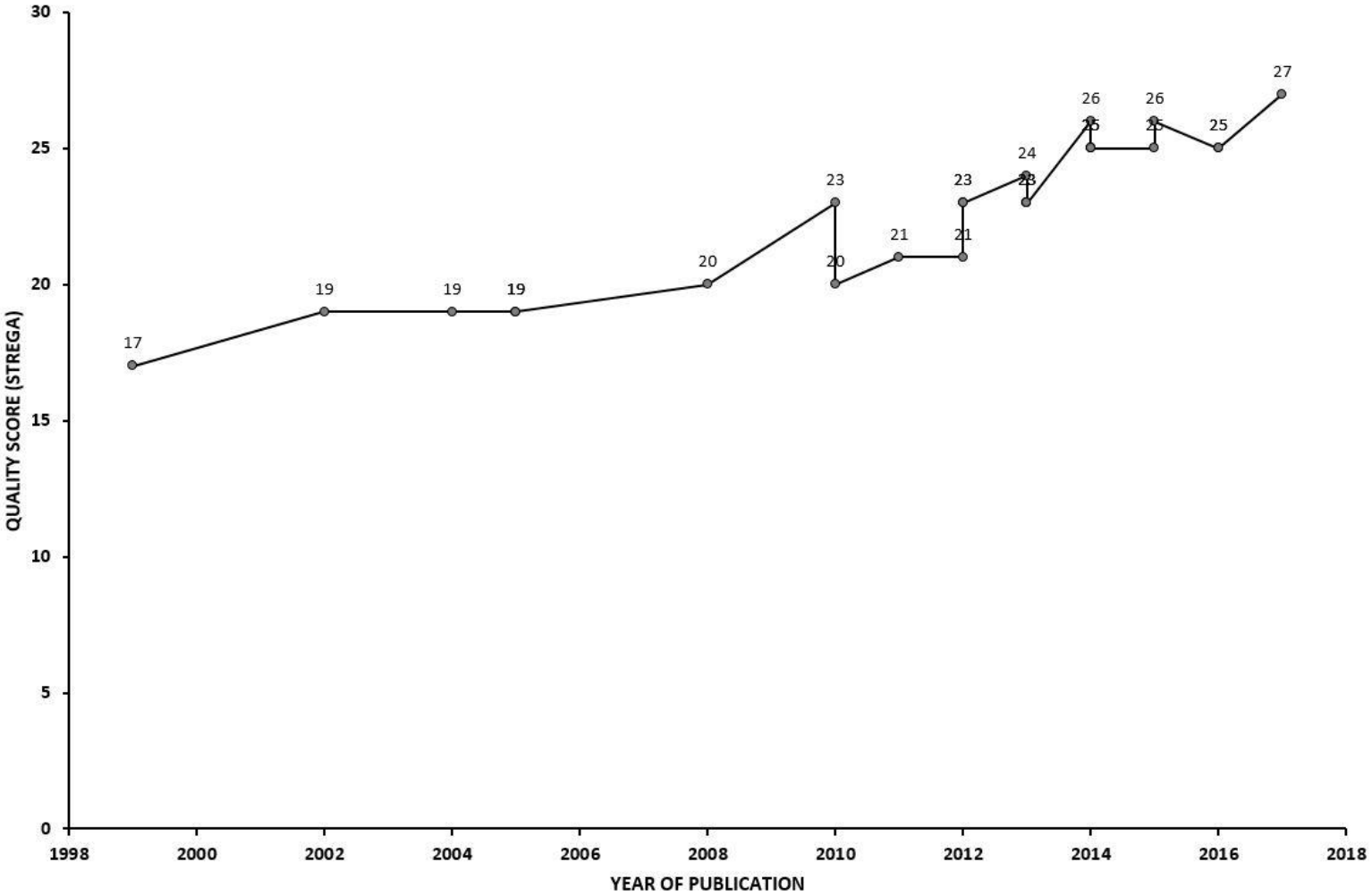
Main results	22 23 24 25	Multiple test correction – appropriate threshold depends on study design Statistical model adjustment and other interactions Covariate adjusted and unadjusted model results Significant results before and after adjusting the model
Discussion		
Key results	26	Whether results supported the study hypothesis or not
Limitations	27	Presented strength and weakness of the study
Interpretation	28	Any previous evidence supported the study outcomes, novel result, how it is assessing the risk and clinical points
Generalization	29	Replication / validation of the results
Other information		
Funding	30	Funding source disclosures

Table S5. Risk bias assessment of genetic association studies using STREGA guidelines

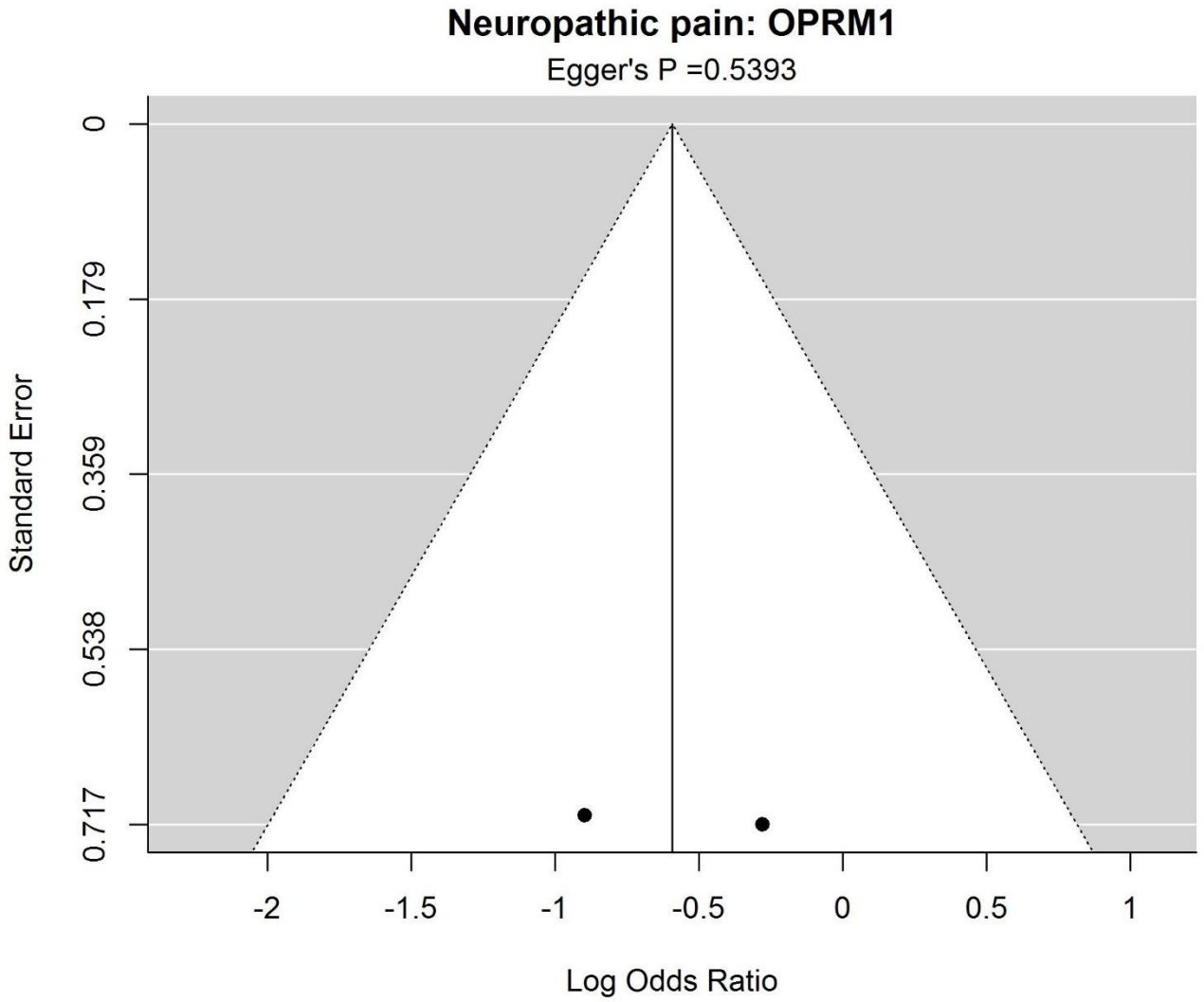
Study	Title & Abstract (Max. score =1)	Introduction (Max. score =2)	Study selection (Max. score =9)	Statistical methods (Max. score =4)	Outcomes (Max. score =9)	Discussion (Max. score =4)	Funding (Max. score =1)	Quality score (Max. score =30)
Armero *et al.*	1	2	7	2	3	3	1	19
Binder *et al.*	1	2	9	3	2	4	0	21
Cheng *et al.*	1	2	8	3	5	3	1	23
Chung *et al.*	1	2	7	3	7	4	1	25
Cui et al.	1	2	9	3	7	3	1	26
Dominguez *et al.*	1	2	9	2	6	3	1	24
Fernandez-de-las-Penas C et al.	1	2	9	3	5	3	0	23
Fernandez-de-las-Penas *et al.*	1	2	8	3	6	3	0	23
Hegarty *et al.*	1	2	7	2	5	3	1	21
Jacobsen *et al.*	1	2	9	3	5	3	0	23
Jacobsen M *et al.*	1	2	8	3	6	3	0	23
Kallianpur *et al.*	1	2	8	3	7	3	1	25
Kalliomaki *et al.*	1	2	9	3	6	4	0	25
Li *et al.*	1	2	9	2	7	3	1	25
Meng *et al.*	1	2	8	4	7	3	0	25
Meng *et al.*	1	2	8	4	7	3	1	26
Nissenbaum *et al.*	1	2	7	2	5	2	1	20

Noponen-Hietala *et al.*	1	2	8	2	3	2	1	19
Ozawa *et al.*	1	2	5	2	4	2	1	17
Sato *et al.*	1	2	7	2	4	2	1	19
Sato-Takeda *et al.*	1	2	7	2	4	2	1	19
Stephens *et al.*	1	2	7	4	7	3	1	25
Sumiyama *et al.*	1	2	6	2	6	3	0	20
Wadley *et al.*	1	2	8	4	6	2	0	23
Warner et al.	1	2	8	4	7	4	1	27

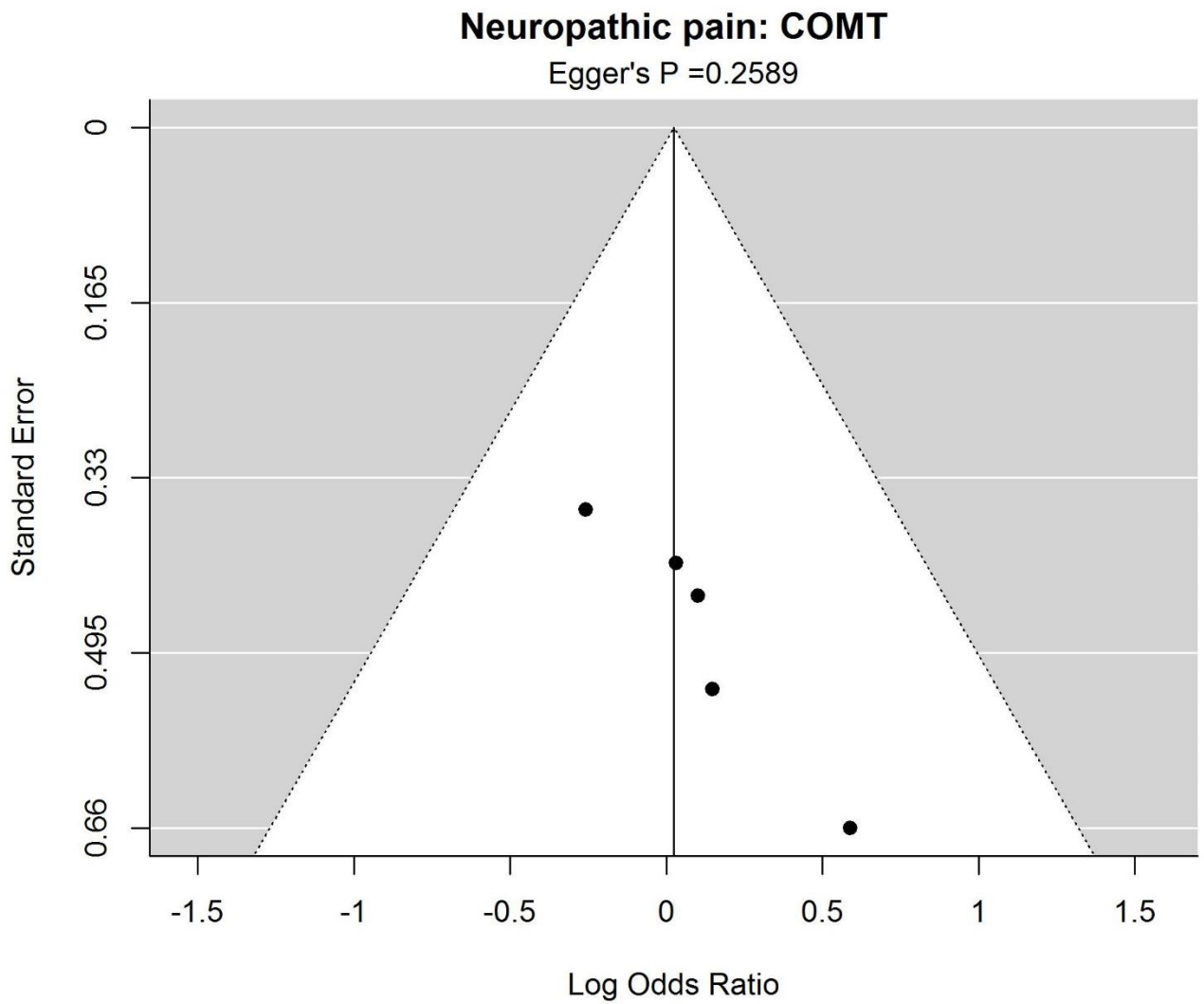
Supplementary Figures



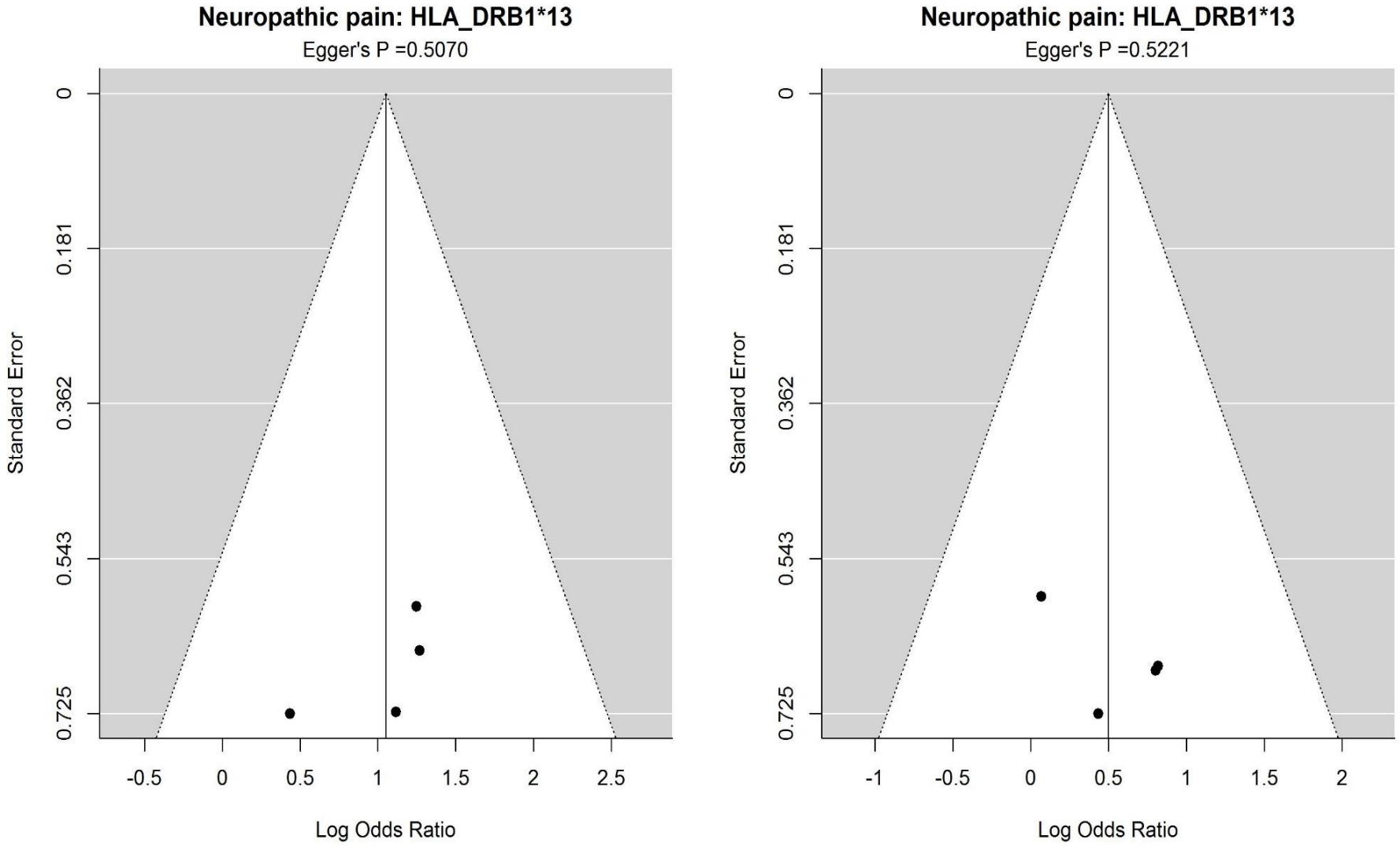
Supplementary Figure S1. Quality score according to STREGA (Strengthening the reporting of genetic association studies) guidelines for each published genetic association studies in neuropathic pain until April 2017. Maximum quality score is 30.



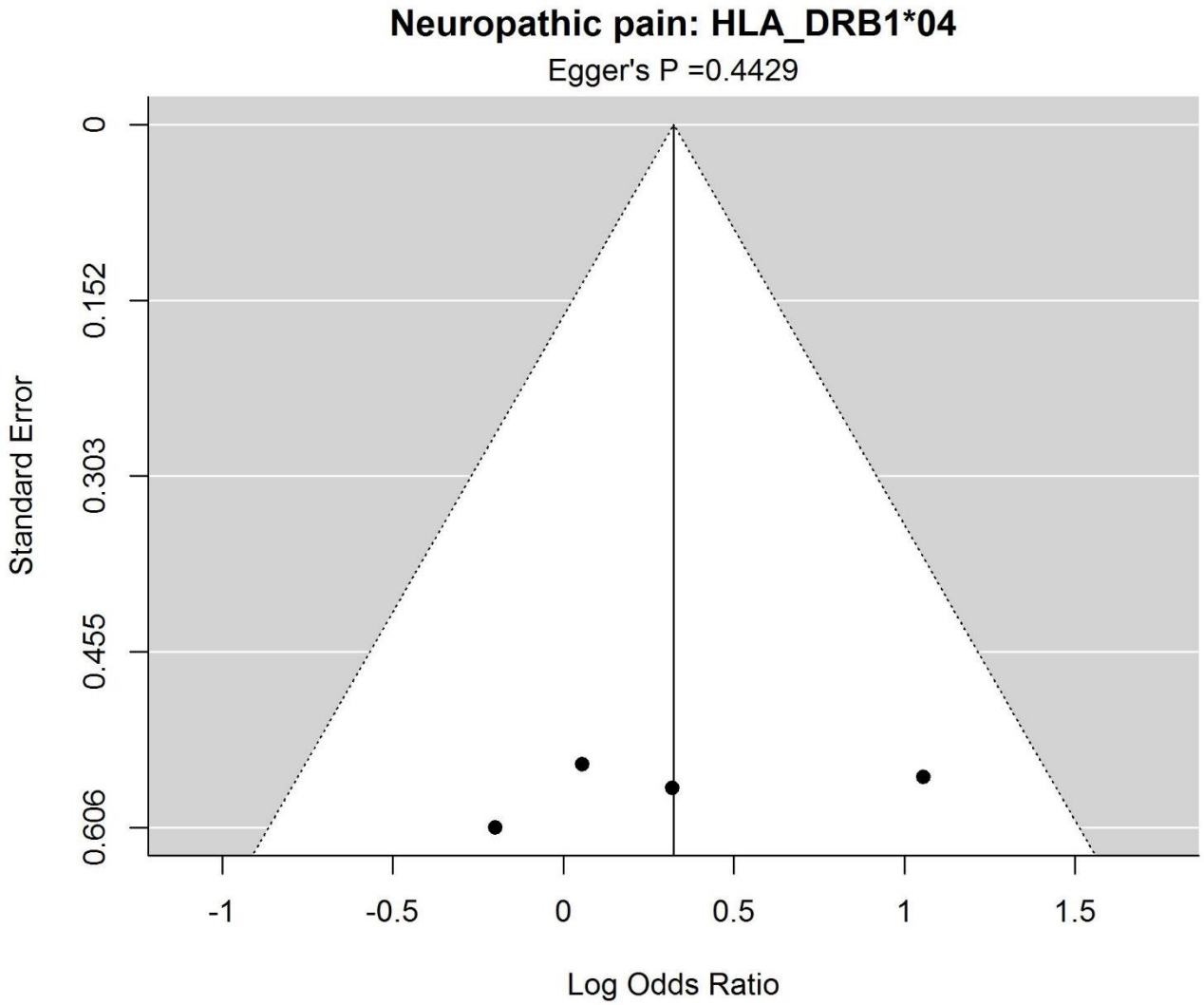
Supplementary Figure S2. Funnel plot of SE against log OR for OPRM1 variant.



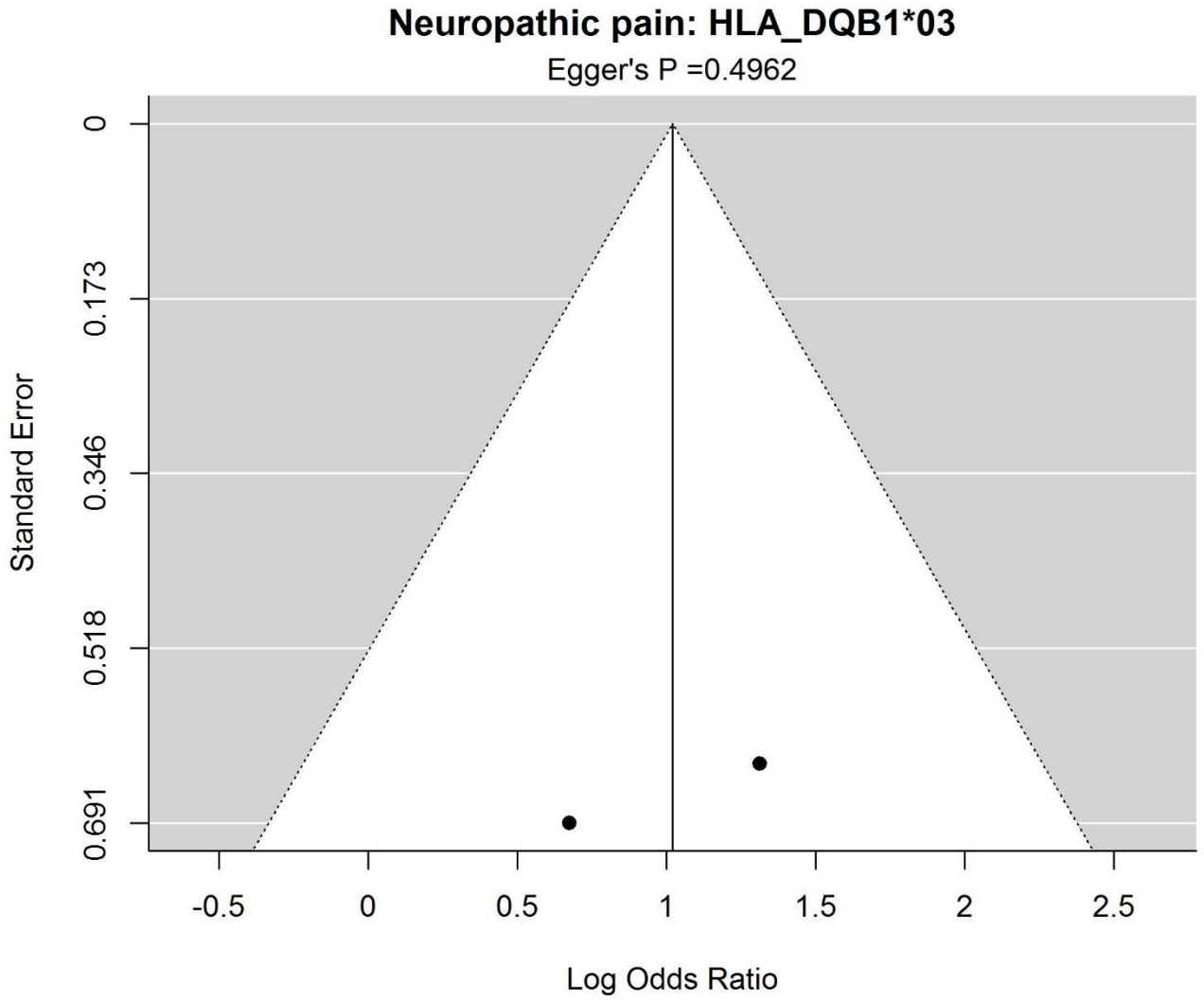
Supplementary Figure S3. Funnel plot of SE against log OR for COMT variant.



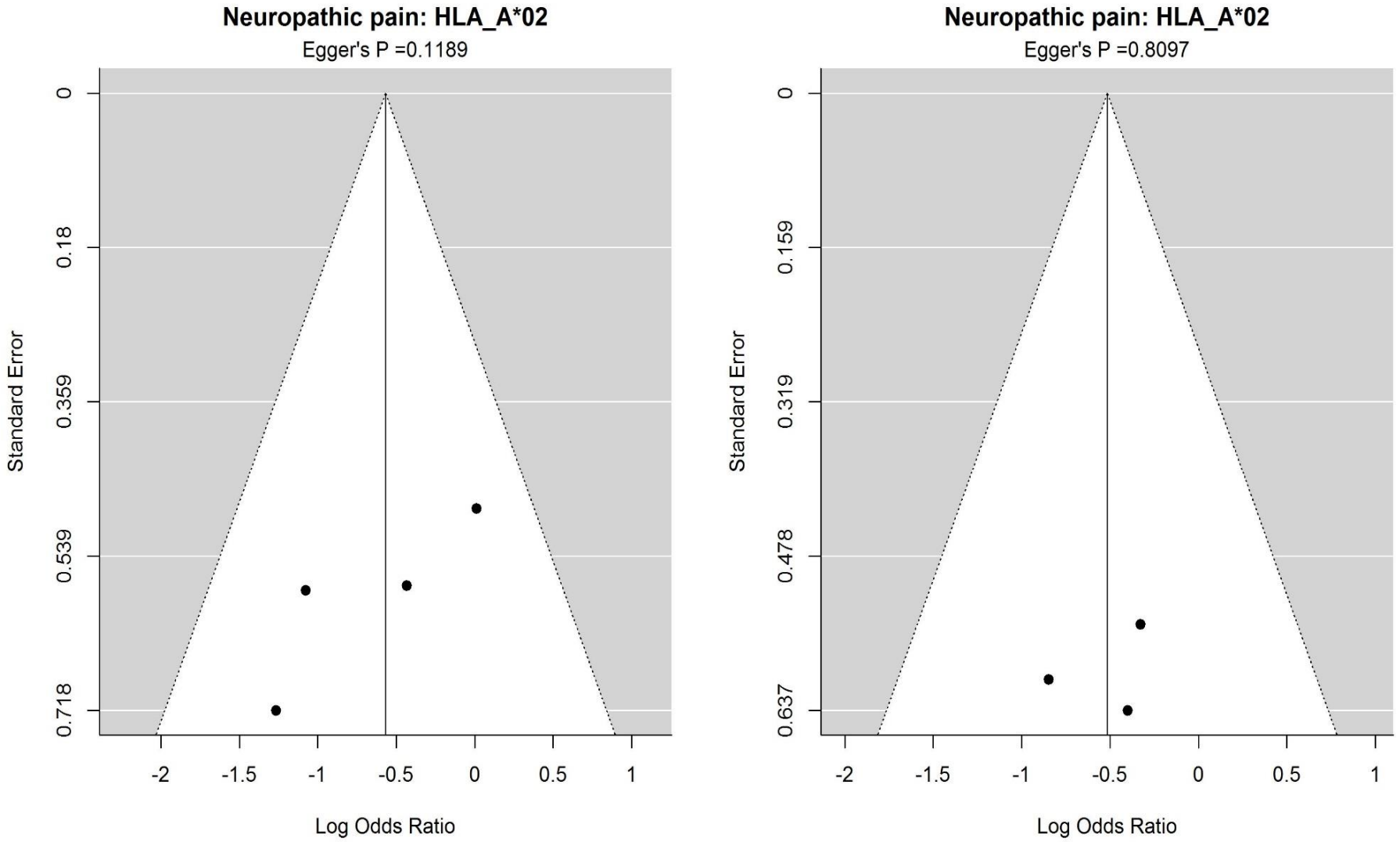
Supplementary Figure S4. Funnel plots of SE against log OR for HLA-DRB1*13. Left, NP (PHN) vs. controls; Right, NP (PHN) vs. participants without PHN.



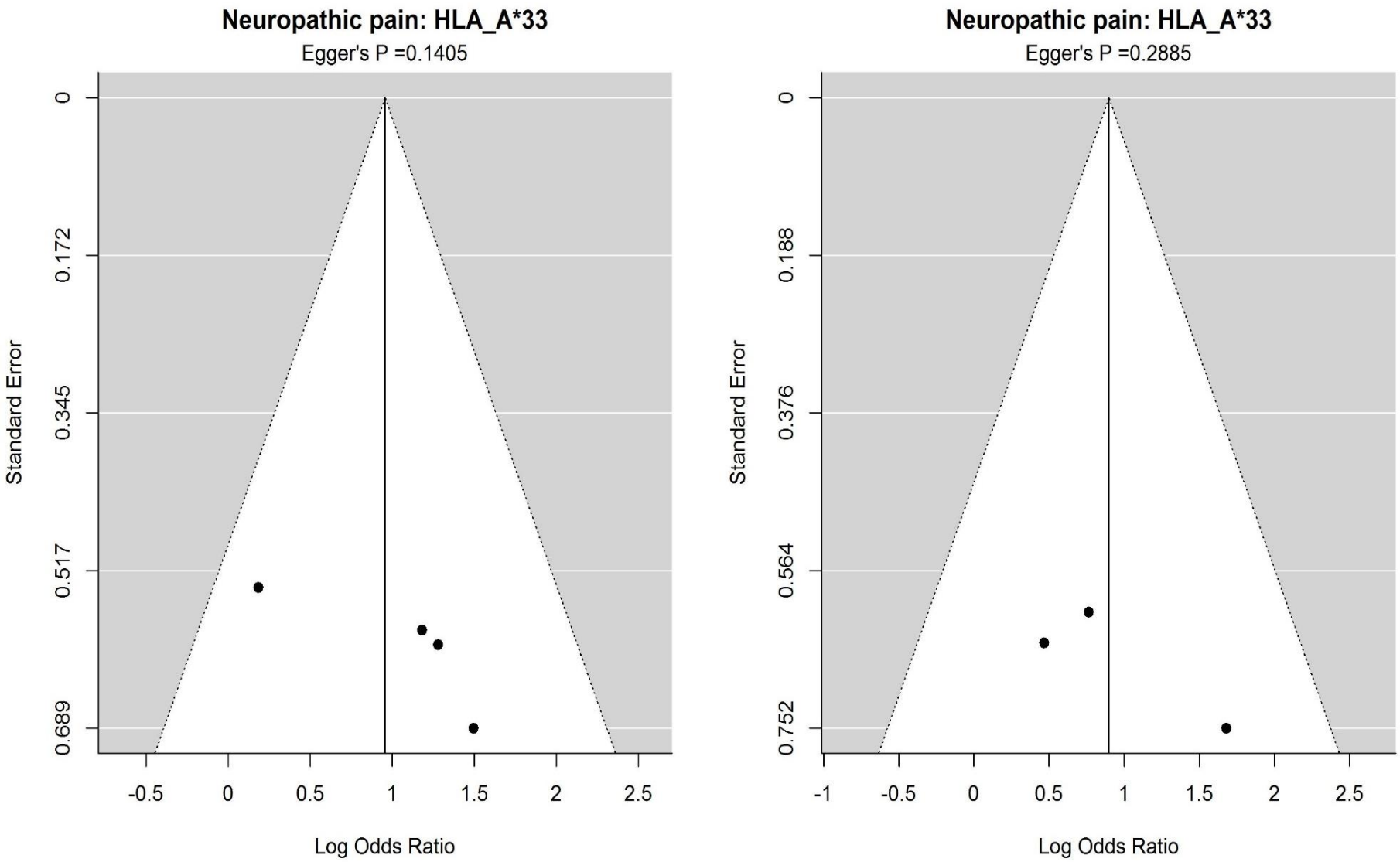
Supplementary Figure S5. Funnel plots of SE against log OR for HLA-DRB1*04.



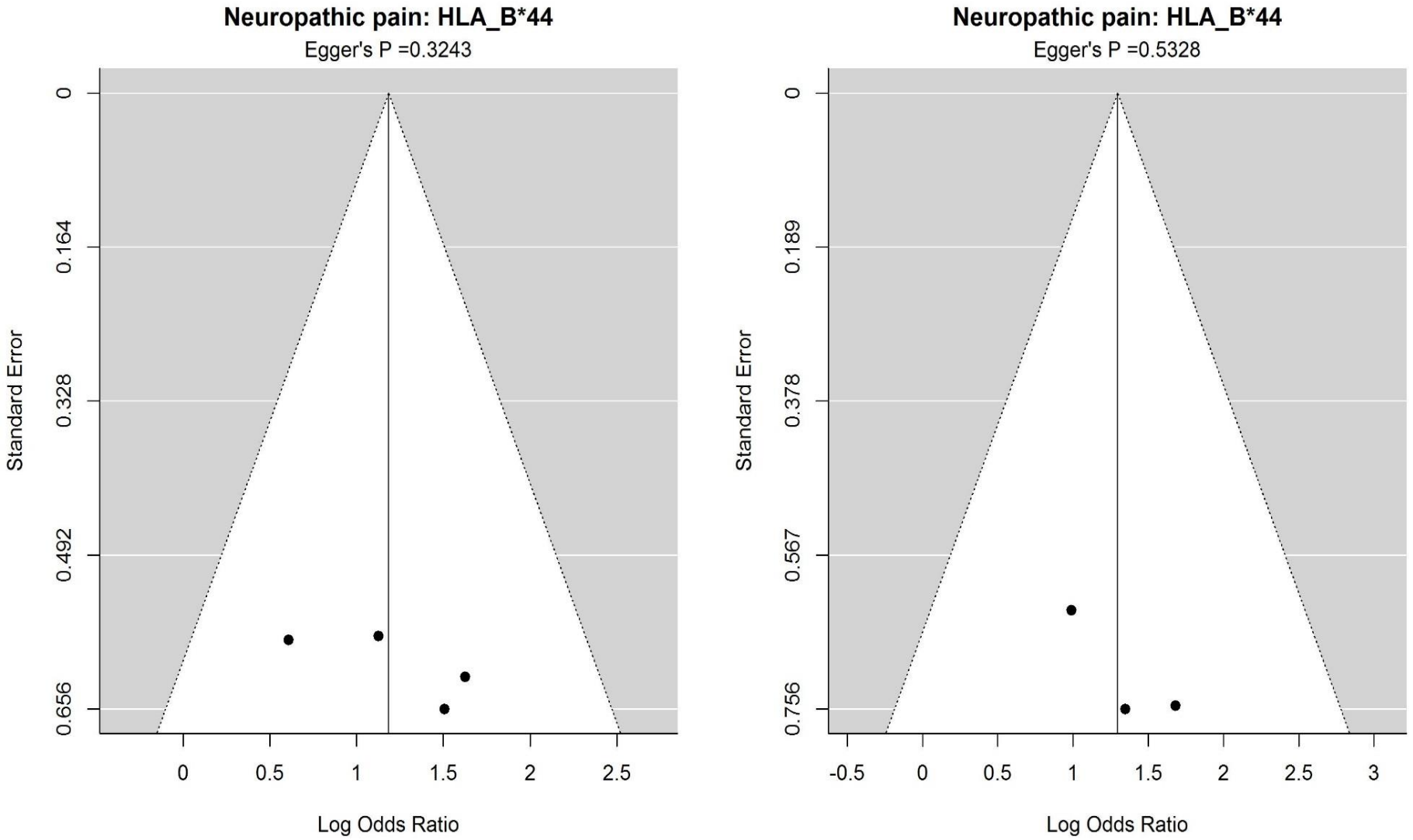
Supplementary Figure S6. Funnel plots of SE against log OR for HLA-DQB1*03.



Supplementary Figure S7. Funnel plots of SE against log OR for HLA-A*02. Left, NP vs. controls; Right, NP vs. participants without PHN.



Supplementary Figure S8. Funnel plots of SE against log OR for HLA-A*33. Left, NP (PHN) vs. controls; Right, NP (PHN) vs. participants without PHN.



Supplementary Figure S9. Funnel plots of SE against log OR for HLA-B*44. Left, NP (PHN) vs. controls; Right, NP (PHN) vs. participants without PHN.

Open Access License Agreement

This OPEN ACCESS LICENSE AGREEMENT (this "Agreement"), dated as of.

20th November 2017

DATE

(the "Effective Date"), by and between Wolters Kluwer Health, Inc., operating as Medical Research / Lippincott Williams & Wilkins, a Delaware corporation, having its principal place of business at Two Commerce Square, 2001 Market Street, Philadelphia, PA 19103 (the "Publisher"), and the corresponding author listed on Schedule A to this Agreement (the "Author", and together with the Publisher, the "Parties").

1. Grant of License

The Author hereby grants to the Publisher and its Affiliates the exclusive, worldwide, royalty free, perpetual (for the duration of the applicable copyright) right and license to use the Work for all commercial or educational purposes, including, but not limited to, publishing, reproducing, marketing, distributing (themselves and through distributors), sublicensing, and selling copies of the Work throughout the world for the Term. If the Author is a United States government employee, such license grant shall be limited to the extent the Author is able to grant such license.

2. Warranties, Indemnification, and Limitation of Liability

a. The Author represents and warrants that:

(i) it has the right and power to enter into this Agreement, to grant the rights and licenses granted pursuant to this Agreement, and to perform all of its other obligations contained in this Agreement;

(ii) it has not previously assigned, transferred or otherwise encumbered the rights or licenses granted pursuant to this Agreement; and that the person executing this Agreement on the Author's behalf is authorized to do so;

(iii) the Work and the licenses granted herein do not and will not infringe upon, violate or misappropriate any intellectual property rights or any other proprietary right, contract or other right or interest of any third party;

(iv) if the Work is a multi-authored Work, the Author has obtained written permission from each author of the Work to enter into this Agreement on behalf such author, and each such author has read, understands and has agreed to the terms of this Agreement; and

(v) the Author has obtained any necessary releases and permissions to quote from other sources in the Work and to include any works and materials in the Work and all such releases and permissions are in full force and effect.

b. The Author hereby indemnifies the Publisher and its directors, officers, employees, agents, and representatives and agrees to defend and hold them harmless from and against any and all liability, damage, loss, costs or expenses (including reasonable attorney's fees and costs of settlement) incurred by any such party arising out of, or relating to any misrepresentation in, or breach or alleged breach of the Author's representations or warranties in this Agreement. If the Author fails to promptly or diligently pursue any defense of any indemnified party, the indemnified parties, or any of them, may assume such defense at the Author's expense. The obligations of this indemnification will survive any termination or expiration of this Agreement.

c. The Publisher represents and warrants that it has the right and power to enter into this Agreement and to perform its obligations contained in this Agreement, and that the person executing this Agreement on the Publisher's behalf is authorized to do so.

d. The Publisher hereby indemnifies the Author and agrees to defend and hold the Author harmless from and against any and all liability, damage, loss, costs or expenses (including reasonable attorney's fees and costs of settlement) incurred by the Author arising out of, or relating to any misrepresentation in, or breach or alleged breach of the Publisher's representations or warranties in this Agreement. If the Publisher fails to promptly or diligently pursue any defense of the Author, the Author may assume such defense at the Publisher's expense. The obligations of this indemnification will survive any termination or expiration of this Agreement.

e. EXCEPT AS OTHERWISE SET FORTH IN THIS AGREEMENT, NEITHER PARTY MAKES ANY OTHER, AND HEREBY DISCLAIMS ALL OTHER, REPRESENTATIONS AND WARRANTIES OF ANY KIND, WHETHER EXPRESS, IMPLIED, STATUTORY OR OTHERWISE, INCLUDING, WITHOUT LIMITATION, WARRANTIES OF TITLE, MERCHANTABILITY, FITNESS FOR A PARTICULAR PURPOSE, NONINFRINGEMENT, OR THE ABSENCE OF LATENT OR OTHER DEFECTS, ACCURACY, OR THE PRESENCE OR ABSENCE OF ERRORS, WHETHER OR NOT DISCOVERABLE.

f. EXCEPT TO THE EXTENT REQUIRED BY APPLICABLE LAW, IN NO EVENT WILL EITHER PARTY BE LIABLE TO THE OTHER PARTY BASED UPON ANY LEGAL THEORY FOR ANY SPECIAL, INCIDENTAL, CONSEQUENTIAL, PUNITIVE, OR EXEMPLARY DAMAGES ARISING OUT OF THIS LICENSE OR THE USE OF THE WORK, EVEN IF A PARTY HAS BEEN ADVISED OF THE POSSIBILITY OF SUCH DAMAGES.

3. Creative Commons License.

Creative Commons Licenses are subject to items selected in item 1, 2 and 3 in the Schedule B.

a. CCBY-NC-ND – NonCommercial-NonDerivitives Creative Commons License

The Author acknowledges and agrees that the Work will be published by the Publisher in (the "Journal") and made freely available to users under the terms of the Attribution-NonCommercial-NoDerivs 4.0 Creative Commons License, as currently displayed at http://creativecommons.org/licenses/by-nc-nd/4.0/legalcode (the "CC BY-NC-ND"). The Author acknowledges and agrees that that Publisher is the exclusive "Licensor", as defined in the CC BY-NC-ND, of the Work and that the Publisher may make the Work freely available to all users under the terms of the CC BY-NC-ND.

b. CCBY – Creative Commons License

The Author acknowledges and agrees that the Work will be published by the Publisher in (the "Journal") and made freely available to users under the terms of the Attribution 4.0 Creative Commons License, as currently displayed at http://creativecommons.org/licenses/by/4.0/legalcode (the "CC BY"). The Author acknowledges and agrees that that Publisher is the exclusive "Licensor", as defined in the CC BY, of the Work and that the Publisher may make the Work freely available to all users under the terms of the CC BY.

c. CCBY-NC – NonCommercial Creative Commons License

The Author acknowledges and agrees that the Work will be published by the Publisher in (the "Journal") and made freely available to users under the terms of the Attribution-NonCommercial 4.0 Creative Commons License, as currently displayed at http://creativecommons.org/licenses/by-nc/4.0/legalcode (the "CC BY-NC"). The Author acknowledges and agrees that that Publisher is the exclusive "Licensor", as defined in the CC BY-NC, of the Work and that the Publisher may make the Work freely available to all users under the terms of the CC BY-NC.

4. Royalties.

The Author acknowledges and agrees that this Agreement entitles the Author to no royalties or fees. To the maximum extent permitted by law, the Author waives any and all rights the Author may have to collect royalties or other fees in relation to the Work or in respect of any use of the Work by the Publisher or its sublicensees.

5. Miscellaneous.

a. Assignment. This Agreement may not be assigned or transferred, in whole or in part, by either party without the prior written consent of the other party. Notwithstanding the above, the Publisher may assign this Agreement without the written consent of the Author (i) to an entity succeeding, whether by sale, merger or other corporate reorganization,

to substantially all of the Publisher's assets and business activity, or (ii) to a corporation or organization that obtains the right to publish the Journal from the Publisher. The Publisher may assign this Agreement to any of its affiliates. This Agreement will be binding upon and inure to the benefit of the parties hereto and their respective successors and permitted assigns.

b. Counterparts. This Agreement may be executed in two or more counterparts, each of which shall be deemed an original, but all of which together shall constitute one and the same document. Facsimile or Portable Document Format (PDF) signatures will be deemed original signatures for purposes of this Agreement.

c. Entire Agreement; Amendment. This Agreement sets forth the entire agreement of the parties on the subject hereof and supersedes all previous or contemporaneous oral or written representations or agreements relating to the rights and duties provided herein, and may not be modified or amended except by written agreement of the parties.

d. Force Majeure. Neither party shall be liable for any default or delay on its part in performing any obligation under this Agreement if such default or delay is caused by natural disaster, accident, war, civil disorder, strike or any other cause beyond the reasonable control of such party. In the event that either party is prevented by such an occurrence or circumstance for a period of more than ninety (90) days from fulfilling its obligations under this Agreement, the other party may terminate this Agreement upon thirty (30) days' written notice.

e. Governing Law. This Agreement shall be governed in all respects according to the laws of the State of New York without giving effect to the principles of conflict of law thereof.

f. Headings. All headings are for reference purposes only and shall not affect the meaning or interpretation of any provision hereof.

g. Severability. If any provision of this Agreement is held to be illegal, invalid, or unenforceable under the present or future laws, then such provision shall be revised by a court of competent jurisdiction to be enforceable if permitted under applicable law, and otherwise shall be fully severable. In any event, this Agreement shall be construed and enforced as if such illegal, invalid, or unenforceable provision had never comprised a part of this Agreement, and the remaining provisions of this Agreement shall remain in full force and effect and shall not be affected by the illegal, invalid, or unenforceable provision or by its severance from this Agreement.

h. Status of the Parties. The parties are independent contractors. Nothing in this Agreement is intended to or shall be construed to constitute or establish any agency, joint venture, partnership or fiduciary relationship between the parties, and neither party has the right or authority to bind the other party nor shall either party be responsible for the acts or omissions of the other.

i. Waiver; Amendment. The waiver by either party of or the failure by either party to claim a breach of any provision of this Agreement shall not be, or be held to be, a waiver of any subsequent breach or affect in any way the further effectiveness of any such provision. No term or condition of this Agreement may be waived except by an agreement by the parties in writing.

j. Waiver of Jury Trial. EACH PARTY HEREBY WAIVES ITS RIGHT TO A JURY TRIAL IN CONNECTION WITH ANY DISPUTE OR LEGAL PROCEEDING ARISING OUT OF THIS AGREEMENT OR THE SUBJECT MATTER HEREOF.

[Signature Page Follows]

Schedule A

This Schedule A must be completed by Author in its entirety. The Publisher is unable to publish the Work unless this Schedule A is completely filled out.

PAIN-D-17-00936

Article Tracking #

Systematic review and meta-analysis of genetic risk factors for neuropathic pain

Article Title (the "Work")

Blair H. Smith

Corresponding Author Name (the "Author")

Wolters Kluwer

Copyright Owner's Name

Pain

Name of Journal in which Work is to be Published

Schedule B

This Schedule B must be completed by Author in its entirety. The Publisher is unable to publish the Work unless this Schedule B is completely filled out.

MANDATED FUNDING POLICY DISCLOSURE

1. Choose a funder from the drop down list. If any of the following are selected please complete Item 2.

Wellcome Trust

NOTE: If you are a World Health Organization Employee and are required to publish under the Creative Commons CCBY IGO license, then do not complete this form. Instead, please contact the Editorial Office for the separate WHO Employee license agreement.

2. If you have selected funding from the above list in 1., please disclose the Open Access option to which the Work will be subject. Selecting "Gold Route" will ensure that your work is published under the Creative Commons CCBY license.

☑ Gold route

☐ Green route

NOTE: If the "Gold" route has been selected, Section 3.b. of the Agreement will apply to the Work, and neither Section 3.a. nor Section 3.c. of the Agreement will apply to the Work. If the "Green" route has been selected, Section 3.c. of the Agreement will apply to the Work after an embargo, and neither Section 3.a. nor Section 3.b. of the Agreement will apply to the Work.

3. ☑ This Schedule B is inapplicable to the Work.

NOTE: If author has selected Item 3, Section 3.a. on the Agreement will apply to the Work, and neither Section 3.b. nor Section 3.c. of the Agreement will apply to the Work.

GOVERNMENT EMPLOYEES

4. ☐ This work was created in the course of an author's employment by the United States Government

If the Work or a portion of it has been created in the course of any author's employment by the United States Government, check the "Government" box at the end of this form. A work prepared by a government employee as part of his or her official duties is called a "work of the U.S. Government" and is not subject to copyright. If it is not prepared as part of the employee's official duties, it may be subject to copyright.

If "Government" is chosen, please do not choose a Creative Commons License. The work will be published with "Written work prepared by employees of the Federal Government as part of their official duties is, under the U.S. Copyright Act, a "work of the United States Government" for which copyright protection under Title 17 of the United States Code is not available. As such, copyright does not extend to the contributions of employees of the Federal Government."

NOTE: If author has selected Item 4, Section 3. on the Agreement will not apply to the Work.

SIGNATURE PAGE

The Corresponding Author acknowledges and agrees that the Corresponding Author is entering into, and has executed, the Agreement on behalf of the Corresponding Author and each other author named as contributing to the Article (each such author, an "Author", and collectively, the "Authors"). The Corresponding Author represents and warrants that the Corresponding Author has obtained permission from each Author to enter into the Agreement on behalf of such Author and the Corresponding Author and each Author has read, understands, and has agreed to the terms of the Agreement, including, without limitation, the terms contained in the Agreement with respect to authorized reuse of the Article.

IN WITNESS WHEREOF, the Author has executed this License, effective as of the Effective Date.

Blair H. Smith

PRINT NAME

Blair H. Smith Digitally signed by Blair H. Smith
Date: 2017.11.25 13:16:08 Z

SIGNATURE

Important Note: Once you electronically sign this form, you will not be able to make any additional changes to it.

To electronically sign this form, click the signature field above and provide the information requested in the dialog boxes.

Please wait...

If this message is not eventually replaced by the proper contents of the document, your PDF viewer may not be able to display this type of document.

You can upgrade to the latest version of Adobe Reader for Windows®, Mac, or Linux® by visiting http://www.adobe.com/go/reader_download.

For more assistance with Adobe Reader visit http://www.adobe.com/go/acrreader.

Please wait...

If this message is not eventually replaced by the proper contents of the document, your PDF viewer may not be able to display this type of document.

You can upgrade to the latest version of Adobe Reader for Windows®, Mac, or Linux® by visiting http://www.adobe.com/go/reader_download.

For more assistance with Adobe Reader visit http://www.adobe.com/go/acrreader.

Please wait...

If this message is not eventually replaced by the proper contents of the document, your PDF viewer may not be able to display this type of document.

You can upgrade to the latest version of Adobe Reader for Windows®, Mac, or Linux® by visiting http://www.adobe.com/go/reader_download.

For more assistance with Adobe Reader visit http://www.adobe.com/go/acrreader.

Please wait...

If this message is not eventually replaced by the proper contents of the document, your PDF viewer may not be able to display this type of document.

You can upgrade to the latest version of Adobe Reader for Windows®, Mac, or Linux® by visiting http://www.adobe.com/go/reader_download.

For more assistance with Adobe Reader visit http://www.adobe.com/go/acrreader.

Please wait...

If this message is not eventually replaced by the proper contents of the document, your PDF viewer may not be able to display this type of document.

You can upgrade to the latest version of Adobe Reader for Windows®, Mac, or Linux® by visiting http://www.adobe.com/go/reader_download.

For more assistance with Adobe Reader visit http://www.adobe.com/go/acrreader.